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Screening Asymptomatic Adults for Coronary Heart Disease With Resting or Exercise Electrocardiography: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: Coronary heart disease is the leading cause of death in the United States in adults. Traditional risk factors do not account for all of the excess risk associated with coronary heart disease. Screening for abnormalities with resting or exercise electrocardiography (ECG) could help identify persons at higher risk for coronary heart disease who might benefit from interventions to reduce cardiovascular risk.

Purpose: To update the 2004 U.S. Preventive Services Task Force (USPSTF) evidence review on screening for resting or exercise ECG abnormalities in asymptomatic adults.

Data Sources: We searched Ovid MEDLINE from January 2002 through January 2011 and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through the fourth quarter of 2010. We supplemented electronic searches with reviews of reference lists, including prior USPSTF reviews.

Study Selection: We included randomized controlled trials and prospective cohort studies that evaluated benefits or harms of screening compared with no screening in asymptomatic adults, or evaluated use of interventions to reduce cardiovascular risk (lipid-lowering therapy and aspirin) in screened persons compared with unscreened persons. We included prospective cohort studies that evaluated the usefulness of screening for abnormalities with resting or exercise ECG for predicting subsequent cardiovascular events, after controlling for at least five of the seven Framingham risk factors.

Data Extraction: Data were abstracted by two investigators and discrepancies were resolved by consensus. Quality was assessed based on methods developed by the USPSTF.

Data Synthesis (Results): No study evaluated benefits of screening compared with no screening, or use of lipid-lowering therapy or aspirin following screening. No study estimated effects of screening on reclassification. Two studies found that resting or exercise ECG findings plus traditional risk factor assessment resulted in a slight increase in the C statistic compared with traditional risk factor assessment alone.

Twenty-seven prospective cohort studies (10 rated good quality) with over 170,000 subjects evaluated resting ECG abnormalities and 38 prospective cohort studies (19 rated good quality) with over 90,000 subjects evaluated exercise ECG abnormalities as predictors of subsequent cardiovascular events, after adjusting for traditional risk factors. Pooled analyses showed that abnormalities on resting (ST segment abnormalities, T wave abnormalities, ST segment or T wave abnormalities, left ventricular hypertrophy, bundle branch block, left axis deviation) or exercise (ST segment depression with exercise, failure to reach maximum target heart rate, low exercise capacity or fitness) ECG were associated with increased risk of subsequent cardiovascular events, after adjusting for traditional risk factors (pooled hazard ratio estimates from 1.4 to 2.1).

Evidence on direct harms associated with screening with resting or exercise ECG is very limited, but direct harms appear minimal (resting ECG) or small (exercise ECG). No study estimated

risks of downstream harms associated with subsequent testing or interventions, though rates of angiography after exercise ECG ranged from 0.6 to 2.9 percent.

Limitations: We only included English-language studies. Statistical heterogeneity was present in several of the pooled analyses.

Conclusions: Abnormalities on resting or exercise ECG are associated with an increased risk of subsequent cardiovascular events after adjusting for traditional risk factors, but the clinical implications of these findings are unclear.

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Chapter 1. Introduction

Scope and Purpose

Coronary heart disease (CHD) is the leading cause of death in the United States in both men and women, accounting for nearly 40 percent of all deaths each year.[1,2] Each year, more than 1 million Americans experience nonfatal or fatal myocardial infarction (MI) or sudden death from CHD. Although angina is a common presenting symptom of CHD, in some persons the first manifestation of CHD is MI, sudden death, or another serious cardiovascular event. (See **Appendix A** for a list of all abbreviations included in this report.)

The risk for incident CHD in asymptomatic persons can be predicted based on the "traditional" risk factors included in the Framingham risk score (age, sex, blood pressure, serum total cholesterol level, low-density lipoprotein [LDL] or high-density lipoprotein [HDL] cholesterol level, cigarette smoking, and diabetes). However, these factors do not explain all of the excess risk.[3,4] Consequently, there has been a long-standing interest in supplementing traditional risk factor assessment with other methods of screening for CHD, including resting or exercise electrocardiography (ECG). Abnormal findings on ECG might identify those at higher risk of CHD events who would not be identified based on traditional risk factors alone.[5] For example, based on the Framingham risk scoring system, persons at intermediate risk are typically defined as having a 10 to 20 percent risk for CHD death or nonfatal MI over 10 years. Abnormal findings on resting or exercise ECG could reclassify some of these persons as low risk (10-year risk <10 percent) and others as high risk (10-year risk >20 percent). Such reclassification, if accurate, could guide use of more aggressive cardiovascular risk reduction therapies in persons reclassified as high risk, which might reduce future CHD events.[6] However, direct evidence showing benefits associated with implementation of such strategies is lacking, and the classification thresholds remain somewhat arbitrary.

The U.S. Preventive Services Task Force (USPSTF) last reviewed the evidence on screening for CHD with resting or exercise ECG in 2004.[7,8] The USPSTF commissioned an update of the evidence review in 2009 in order to revisit its recommendation on screening with resting or exercise ECG. The purpose of this report is to systematically evaluate the current evidence on whether screening asymptomatic adults for CHD with resting or exercise ECG improves clinical outcomes, affects use of risk reduction therapies, or results in accurate reclassification into different risk categories. This report also systematically reviews the evidence on harms associated with screening. In addition to including new evidence, this report differs from earlier USPSTF reviews by focusing on studies that assessed the usefulness of screening after adjusting for traditional cardiovascular risk factors, in order to better understand the incremental value of resting or exercise ECG. In addition, we performed meta-analysis on the association between selected resting and exercise ECG abnormalities and subsequent cardiovascular events.

Condition Definition

CHD refers to atherosclerosis of the coronary arteries. In patients with CHD, plaques form within the arteries, causing reduced blood flow and/or arterial blockage. Symptoms of CHD

include angina, shortness of breath, and fatigue. However, even high-grade atherosclerosis can be present with no accompanying symptoms. Conversely, CHD events can occur even when only mild-grade atherosclerosis is present. Serious CHD events include MI, stroke, heart failure, and sudden cardiac death.

Prevalence and Burden of Disease

The average annual incidence of first major cardiovascular event increases with older age, from around 7 cases per 1,000 in men ages 35–44 years to 68 cases per 1,000 in men ages 85–94 years. For women, similar incidence rates are observed about 10 years later in life, though the gap narrows with advancing age. Disparities exist with regard to mortality from CHD. Mortality rates are lowest for white women and highest for black men. CHD is a major source of direct and indirect health care costs in the United States. In 2010, projected CHD-related costs were $316 billion.[1]

Etiology and Natural History

CHD is a disease of the coronary arteries, which provide oxygenated blood to the myocardium. CHD typically develops over many years with the deposition of atherosclerotic plaque within the endothelial lining of the epicardial coronary arteries, in conjunction with some degree of inflammation. Atherosclerotic plaque tends to develop focally and often in predisposed segments of the coronary arteries, often at branch points. Acute coronary syndrome, MI, and sudden cardiac death are often associated with plaque rupture and/or intravascular thrombosis associated with plaque and/or plaque rupture. In general, CHD is a progressive disease, although the risk of progression can be reduced by addressing modifiable risk factors (see below). CHD is the leading cause of death in the United States.

Significant CHD has often been considered to be present in individuals who have either experienced a coronary event or who have highly stenotic coronary vessels as evaluated by coronary angiography. However, acute coronary events often occur in vessels that are not severely stenotic, as a consequence of plaque rupture or acute thrombosis. Thus, how to identify CHD among individuals without objective clinical evidence of disease is a challenge, since plaque rupture leading to acute coronary events is not necessarily limited to coronary arteries with a high degree of narrowing. This concept has important implications for screening because most markers for CHD on resting and exercise ECG are probably related to the presence of significant coronary artery stenosis. It also has implications for treatment in individuals identified as being at higher risk. Although such individuals might benefit from treatment of modifiable risk factors, they might not necessarily benefit from revascularization procedures.

Risk Factors

Traditional risk factors for CHD (i.e., those included in Framingham risk models) are male sex, older age, tobacco use, hypertension, dyslipidemia (high total or LDL cholesterol or low HDL cholesterol), and diabetes. Other risk factors for CHD include family history of early CHD, obesity, physical inactivity, atherogenic diet, and presence of prothrombic and proinflammatory

factors. Some risk factors are modifiable, and could be targets for treatment in patients identified as being at higher risk. As of 2003, over one third of all American adults have two or more risk factors for CHD, although rates varied according to age, race, and socioeconomic group.[9] Nearly all CHD events (~90 percent) occur in people with at least one risk factor, and the presence of any risk factor at age 50 years—even those of borderline clinical significance—substantially increases the lifetime risk of experiencing a CHD event.[10,11]

Rationale for Screening/Screening Strategies

Many patients with CHD do not present with symptoms prior to experiencing a significant first CHD event such as sudden cardiac arrest, MI, congestive heart failure (CHF), or unstable angina. In fact, based on observational data, symptoms suggestive of CHD are less accurate than traditional risk factors for predicting 5-year mortality.[12] For screening to be clinically useful, it should provide information beyond that available from assessment of traditional risk factors, which are available to clinicians from demographic information and clinical history. Screening could identify individuals with subclinical CHD who might benefit from earlier or more aggressive treatment of modifiable risk factors, or might be candidates for other treatments (such as revascularization). For risk classification strategies to be effective, screening would ideally accurately stratify individuals into low-, intermediate-, and high-risk groups in order to best guide the use of preventive and other measures.

Interventions/Treatment

Commonly used tests for detecting asymptomatic CHD include resting and exercise ECG. Although the most common method of exercise testing is the exercise treadmill test (ETT), other methods include bicycles and ergometers. Both resting and exercise ECG may show markers of unrecognized previous MI, silent or inducible myocardial ischemia, and other cardiac abnormalities (such as left ventricular hypertrophy [LVH], bundle branch block, or arrhythmia) that may be associated with CHD or predict future CHD events. Other screening tests for CHD include the ankle-brachial index, B-mode carotid Doppler ultrasonography, and cardiac computed tomography (CT), a noninvasive imaging examination for coronary artery atherosclerosis. Most of these tests are considered in other USPSTF reviews.[13-15]

Current Clinical Practice

Resting or exercise ECG screening in low-risk patients is not recommended by any organization (see below). Evidence on current clinical use of resting or exercise ECG to screen asymptomatic patients for CHD is sparse, but anecdotally is performed with some frequency. Routine cardiovascular risk factor screening after age 35 years in men and age 45 years in women, with the goal of addressing modifiable risk factors, is recommended by the American College of Cardiology Foundation and the American Heart Association (AHA).[16] Risk factor screening typically involves using Framingham or other risk prediction tools based on the presence of clinical risk factors.

Recommendations of Other Groups

Numerous organizations recommend against routine screening of asymptomatic adults for CHD with resting or exercise ECG, including the American College of Physicians, American Academy of Family Physicians (AAFP), American College of Cardiology, AHA, American College of Preventive Medicine, and American College of Sports Medicine (ACSM).[17-22] Screening of special populations is recommended by some groups. For example, AAFP recommends screening otherwise low-risk patients who have certain occupations in which undetected CHD could significantly impact the public (e.g., airline pilots), and ACSM recommends screening moderate-risk patients who are beginning a new exercise regimen.[22,23]

Previous USPSTF Recommendation

In 2004, the USPSTF recommended against routine screening with resting ECG or ETT for either the presence of severe coronary artery stenosis or the prediction of CHD events in adults at low risk for CHD events (D recommendation). The USPSTF found insufficient evidence to recommend for or against routine screening with ECG or ETT for either the presence of severe coronary artery stenosis or the prediction of CHD events in adults at increased risk for CHD events (I statement).

Chapter 2. Methods

Key Questions and Analytic Framework

The investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions used to guide this review.[24-26] The analytic framework shows the key questions used to guide the review (**Figure 1**).

Key Question 1. What are the benefits of screening for abnormalities with resting or exercise ECG compared with no screening on CHD outcomes?

Key Question 2. How does the identification of high-risk persons via resting or exercise ECG affect use of treatments to reduce cardiovascular risk?

Key Question 3. What is the accuracy of resting or exercise ECG for stratifying persons into high-, intermediate-, and low-risk groups?

Key Question 4. What are the harms of screening with resting or exercise ECG?

The target population for this review was adult women and men ages 18 years and older without symptoms of CHD. The intervention was resting or exercise (treadmill, bicycle, ergometer, or other method) ECG. To evaluate benefits of screening for asymptomatic CHD, we focused on (in order of preference) CHD death, cardiovascular disease (CVD) death, nonfatal MI, all-cause mortality, stroke, and other cardiovascular outcomes (such as CHF). We evaluated composite cardiovascular outcomes only if a study did not report more specific cardiovascular outcomes. To evaluate use of treatments for reducing cardiovascular risk, we focused on use of lipid-lowering therapy and aspirin, because use of these interventions varies depending on the assessed baseline risk.[27,28] The use of other preventive cardiovascular interventions such as weight loss, smoking cessation, and blood pressure management are largely unaffected by estimated baseline risk.[29-32] To evaluate the usefulness of resting or exercise ECG for risk stratification, we evaluated whether the addition of screening to traditional risk factor assessment resulted in more accurate prediction of persons who experienced subsequent cardiovascular events, or improved the classification of persons into high-, intermediate-, or low-risk groups compared with assessment based on traditional risk factors alone. We also evaluated how the presence of abnormalities on resting or exercise screening ECG affected risk for cardiovascular outcomes after adjustment for traditional risk factors, and likelihood of cardiovascular outcomes. We did not evaluate the accuracy of resting or exercise ECG for identifying the presence or degree of asymptomatic atherosclerosis because of its unclear clinical implications. To evaluate harms of screening, we evaluated rates and consequences of false-positive and false-negative tests, patient anxiety and other psychosocial effects, and unnecessary treatments. We did not review adverse outcomes associated with lipid-lowering therapy and aspirin, as these have been evaluated in other USPSTF reviews.[33,34]

Search Strategies

We searched Ovid MEDLINE from January 2002 through January 2011 and the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through the fourth quarter of 2010 to identify relevant articles. The search of the Cochrane Database of Systematic Reviews failed to identify any publications directly relevant to this report. Complete search strategies are shown in **Appendix B1**. We identified additional studies from citations in relevant articles and experts, and included studies from the previous USPSTF review that met inclusion criteria.

Study Selection

We selected studies based on inclusion and exclusion criteria developed for each key question (**Appendix B2**). All citations were independently reviewed by two investigators before final exclusion. Results of the search and selection process are described in **Appendix B3**.

We included randomized controlled trials and controlled observational studies that evaluated effects of screening with resting or exercise ECG compared with no screening on clinical outcomes (benefits or harms). We also included large uncontrolled studies that reported harms associated with screening resting or exercise ECG. We included studies that evaluated persons without symptoms of CHD, reported results separately for asymptomatic persons, or included persons with symptoms, if the proportion of patients was <10 percent of the total sample. For usefulness of screening for risk stratification, we included prospective cohort studies that reported rates of cardiovascular outcomes and controlled for at least five of the seven Framingham cardiovascular risk factors (male sex, older age, tobacco use, diabetes, hypertension, high total or LDL cholesterol, and low HDL cholesterol) through restriction (e.g., only enrolling male subjects) or adjustment. Many studies of the same cohort were described in multiple publications; a detailed listing of included studies and publications can be found in **Appendix B4**. We excluded a number of studies included in prior USPSTF reviews[7, 8] because they did not adjust for five or more traditional risk factors[35-53] or otherwise did not meet inclusion criteria (**Appendixes B5** and **B6**).[54,55]

Data Abstraction and Quality Rating

One investigator abstracted details about the patient population, study design, analysis, followup, and results; data abstraction was checked by a second investigator. We also recorded how many Framingham risk factors and other confounding factors were adjusted for in the model; whether the investigators reported model fit measures, discrimination measures, or model calibration statistics separately for models with and without resting or exercise ECG; and whether the study assessed the degree and accuracy of reclassification into different risk categories on the basis of ECG findings. Two investigators used criteria developed by the USPSTF[26] to rate the quality of each study as good, fair, or poor. (Criteria used to rate prospective studies on ECG abnormalities and risk of subsequent cardiovascular events are shown in **Appendix B7**; criteria for randomized controlled trials of screening are not shown because no such study met inclusion criteria.) We rated studies as good quality if they met all quality criteria or had only minor methodological

shortcomings. We rated studies as poor quality if they had multiple, important methodological shortcomings. Other studies were rated as fair quality. Discrepancies were resolved through a consensus process.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good," "fair," "poor") using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[26]

We used several methods to assess the incremental value of resting or exercise ECG over traditional Framingham risk factor assessment.[56] We evaluated how the addition of screening with resting or exercise ECG to traditional risk factor assessment affects reclassification of subjects into high- (10-year risk for CHD or nonfatal MI >20 percent), intermediate- (10-year risk 10–20 percent), or low-risk (10-year risk <10 percent) categories compared with classification based on traditional risk factors alone.[57] Reclassification has recently been emphasized in the literature[57-60] because understanding the frequency and accuracy by which people are reclassified into different risk categories is important, and can have a significant effect on clinical decisions.[6,61] Risk stratification tables are one method for comparing the proportion of patients correctly moved from intermediate to low- and high-risk categories using different risk assessment methods.[57]

We also evaluated the C statistic for resting or exercise ECG plus traditional risk factor assessment versus the C statistic based on traditional risk factor assessment alone with regard to prediction of subsequent cardiovascular events. The C statistic is a measure of discrimination, or how accurately a risk assessment method separates those individuals with a disease or outcome from those without it.[62] It indicates the proportion of all pairs of patients (one with and one without the outcome) in which the patient with the outcome has the higher predicted probability of the outcome. We also evaluated whether adding screening ECG improves calibration, or the degree to which predicted and observed risk estimates are in agreement.[59] Compared with measures of discrimination, measures of calibration provide additional information regarding how accurately a risk factor or risk assessment method predicts the likelihood of an outcome in an individual patient. However, measures of discrimination or calibration may be less useful than measures of reclassification for understanding the value of different risk assessment methods, because the former do not necessarily indicate how frequently and accurately people are classified into different risk categories or provide information about the actual predicted risks in an individual patient, which can have important effects on clinical decisions.[6,61]

Most studies did not provide data to estimate the degree and accuracy of reclassification or report measures of discrimination or calibration. Rather, they provided an estimate of the risk of subsequent cardiovascular events associated with resting or exercise ECG abnormalities after adjusting for traditional risk factors. We conducted meta-analysis for ECG abnormalities on adjusted estimates of risk using the DerSimonian-Laird random effects model with Stata 11.1 software (StataCorp, College Station, TX).[63] We focused on CHD death as the preferred outcome, but evaluated other outcomes (CVD death, nonfatal MI, all-cause mortality, or

composite cardiovascular outcomes, in order of preference) if CHD death was not available. We performed meta-analyses for resting or exercise ECG abnormalities that were evaluated by at least three studies. For resting ECG, these abnormalities were ST segment changes, T wave changes, ST segment or T wave changes, LVH, bundle branch block, and left axis deviation. For exercise ECG, these were ST depression with exercise and failure to reach target heart rate. We assessed the presence of statistical heterogeneity using standard chi-square tests and estimated the magnitude of heterogeneity using the I^2 statistic.[64] If at least five studies evaluated an outcome, we evaluated potential sources of heterogeneity by performing pooled analyses and meta-regression on studies stratified according to the outcome evaluated (CHD death or another outcome), study quality (good or fair), and use of different definitions for the abnormality being evaluated. We performed sensitivity analyses, excluding outlier studies if they were present. We also performed meta-regression on the proportion of male subjects enrolled in the study, the number of traditional risk factors that the study adjusted for (ranging from five to seven), and the duration of followup.

External Review

A draft report was reviewed by outside experts, USPSTF members, AHRQ Medical Officers, and federal partners, and was revised based on comments.

Chapter 3. Results

Key Question 1. What are the Benefits of Screening for Abnormalities With Resting or Exercise Electrocardiography Compared With No Screening on Coronary Heart Disease Outcomes?

Summary

We identified no randomized controlled trials or controlled observational studies that reported clinical outcomes of screening for CHD with resting or exercise ECG compared with no screening in asymptomatic adults.

Evidence

Like the previous USPSTF review,[7] we found no randomized controlled trials or controlled observational studies on the effects on clinical outcomes of screening asymptomatic adults for CHD with resting or exercise ECG versus no screening. The prior USPSTF review discussed a subgroup analysis from the Multiple Risk Factor Intervention Trial (MRFIT)[65] that found that subjects with an abnormal ETT who underwent risk factor modification experienced better outcomes compared with those who underwent usual care. However, these findings are not directly applicable to this key question, as they do not address the effects of screening versus no screening.

Key Question 2. How Does the Identification of High-Risk Persons Via Resting or Exercise Electrocardiography Affect Use of Treatments to Reduce Cardiovascular Risk?

Summary

We identified no studies that evaluated how screening individuals using resting or exercise ECG affects use of interventions (e.g., lipid-lowering therapy or aspirin) to reduce cardiovascular risk.

Evidence

Abnormalities on resting or exercise ECG could identify patients who might benefit from interventions to reduce cardiovascular risk, such as lipid-lowering therapy or aspirin. However, like the previous USPSTF review,[7] we identified no studies that evaluated how screening affects use of such interventions.

Key Question 3. What is the Accuracy of Resting or Exercise Electrocardiography for Stratifying Persons Into High-, Intermediate-, and Low-Risk Groups?

Summary

Twenty-seven prospective cohort studies (10 rated good quality) with over 170,000 subjects evaluated resting ECG abnormalities[66-93] and 38 prospective cohort studies (19 rated good quality) with over 90,000 subjects evaluated exercise ECG abnormalities as predictors of subsequent cardiovascular events,[66,78,94-129] after adjusting for traditional risk factors. No study estimated how accurately resting or exercise ECG plus traditional risk factor assessment classified subjects into high-, intermediate-, or low-risk groups compared with classification based on traditional risk factor assessment alone, or provided data to enable the construction of risk stratification tables. One study each reported that resting or exercise ECG findings plus traditional risk factor assessment resulted in a slight increase in discrimination (based on the C statistic) compared with traditional risk factor assessment alone.

Pooled analyses showed that abnormalities on resting (ST segment abnormalities, T wave abnormalities, ST segment or T wave abnormalities, LVH, bundle branch block, left axis deviation) or exercise (ST segment depression with exercise, failure to reach maximum target heart rate) ECG were associated with an increased risk (pooled hazard ratio [HR] estimates from 1.4 to 2.1) of subsequent cardiovascular events, after adjusting for traditional risk factors (**Table 1**). Statistical heterogeneity was present in a number of analyses, but stratification of studies by method of defining the ECG abnormality, study quality, or the type of cardiovascular events evaluated did not reduce heterogeneity and resulted in similar estimates. Meta-regression analyses also showed no effect on estimates based on differential duration of followup, number of Framingham risk factors adjusted for in the analysis, or proportion of male subjects. Low exercise capacity or physical fitness during exercise ECG was also associated with increased risk of subsequent cardiovascular events or all-cause mortality, with hazard ratio estimates ranging from 1.7 to 3.1, but data could not be pooled.

Evidence: Resting ECG

Twenty-seven prospective cohort studies of resting ECG met inclusion criteria (**Table 2**).[66-93] Two studies evaluated both resting and exercise ECG abnormalities.[66,78] Three studies reported results from the Atherosclerosis Risk in Community study,[68,82,83] two studies (reported in three publications) reported results from the Women's Health Initiative,[72,90,91] two studies reported results from the Chicago Heart Association Detection Project in Industry,[76,81] and two studies reported results from the Cardiovascular Health Study.[75,89] Excluding double-counted populations, the studies evaluated a total of 173,710 subjects. Duration of followup ranged from 3[74] to 56 years[69] for resting ECG.

Ten studies were rated as good quality,[66,71-73,75,78,80,87,88,93] and the remainder were rated as fair quality (**Appendix C1**). The most common methodological shortcomings were failure to describe how patients with uninterpretable ECG results were handled (20/27 studies), failure to

describe loss to followup (17/27), and failure to describe race when reporting baseline demographic characteristics (10/27).

Reclassification, calibration, and discrimination. No study estimated how accurately resting ECG plus traditional risk factor assessment classified subjects into high-, intermediate-, or low-risk groups compared with classification based on traditional risk factor assessment alone, or provided data to enable the construction of risk stratification tables.[57] One study of women found that the addition of resting ECG findings to the Framingham risk score increased the C statistic for prediction of CHD events (nonfatal MI or CHD death) from 0.69 (95% confidence interval [CI], 0.61 to 0.86) to 0.74 (95% CI, 0.66 to 0.90), though confidence intervals overlapped.[72]

Adjusted risk estimates.

ST segment abnormalities. Six studies evaluated ST segment abnormalities (defined by various combinations of Minnesota codes 4.1, 4.2, 4.3, and 4.4) on resting ECG as a predictor of subsequent cardiovascular events (**Table 3**).[69,71,76,80,82,86] Two studies evaluated CHD death,[71,76] one study sudden unexpected cardiac death,[69] one study CVD death,[80] and one study nonfatal MI or CHD death.[82] One study focused on stroke as an outcome and was excluded from the meta-analysis.[86] Two studies restricted enrollment to male subjects.[69,86] The proportion of male subjects in the other four studies ranged from 43 to 55 percent.

After adjustment for traditional cardiac risk factors, the pooled hazard ratio for ST segment abnormalities, with regard to subsequent cardiovascular events, was 1.9 (95% CI, 1.4 to 2.5; I^2=62 percent) (**Figure 2**).[69,71,76,80,82] Estimates were similar when studies were stratified according to whether they evaluated CHD death (2 studies; HR, 1.8 [95% CI, 0.76 to 4.5]; I^2=86 percent)[71,76] or another cardiovascular outcome (3 studies; HR, 1.9 [95% CI, 1.5 to 2.4]; I^2=21 percent),[69,80,82] or when studies were stratified according to whether they were rated as good (2 studies; HR, 2.1 [95% CI, 1.2 to 3.6]; I^2=70 percent)[71,80] or fair quality (3 studies; HR, 1.8 [95% CI, 1.1 to 2.8]; I^2=72 percent).[69,76,82] Meta-regression analyses showed that variability in the proportion of male subjects (p=0.92), duration of followup (p=0.67), or the number of traditional risk factors adjusted for (p=0.33) did not explain the between-study variance in hazard ratio estimates. In one study not included in the meta-analysis, ST segment abnormalities were associated with an increased risk of stroke at 0–30 years of followup (HR, 3.4 [95% CI, 2.1 to 5.4]).[86]

T wave abnormalities. Seven studies evaluated T wave abnormalities (defined by various combinations of Minnesota codes 5.1, 5.2, 5.3, and 5.4) (**Table 3**).[69,71,76,80,82,86,88] Three studies evaluated CHD death,[71,76,88] one study CVD death,[80] one study sudden unexpected cardiac death,[69] and one study the combination of nonfatal MI or CHD death.[82] One study focused on stroke as an outcome and was excluded from the meta-analysis.[86] Three studies restricted enrollment to male subjects.[69,86,88] In the other four studies, the proportion of male subjects ranged from 43 to 55 percent. Duration of followup ranged from 10 to 21 years and incidence of CHD or CVD death ranged from 1 to 18 percent.

After adjustment for traditional cardiac risk factors, the pooled hazard ratio for T wave abnormalities, with regard to subsequent cardiovascular events, was 1.6 (95% CI, 1.3 to 1.8;

I^2=56 percent) (**Figure 2**).[69,71,76,80,82,88] Statistical heterogeneity was not reduced and estimates were similar when studies were stratified according to whether they evaluated CHD death (3 studies; HR, 1.5 [95% CI, 1.1 to 1.9]; I^2=52 percent)[71,76,88] or another cardiovascular outcome (3 studies; HR, 1.6 [95% CI, 1.3 to 2.1]; I^2=58 percent),[69,80,82] or when studies were stratified according to whether they were rated as good (3 studies; HR, 1.5 [95% CI, 1.2 to 1.8]; I^2=62 percent)[71,80,88] or fair quality (3 studies; HR, 1.6 [95% CI, 1.2 to 2.2]; I^2=54 percent).[69,76,82] Meta-regression analyses showed that restriction of enrollment to male subjects (p=0.10) and variability in duration of followup (p=0.22) or number of traditional risk factors adjusted for (p=0.66) did not explain the between-study variance in hazard ratio estimates. One study excluded from the meta-analysis found no association between T wave abnormalities and stroke at 0–30 years of followup, though estimates varied depending on the timing of followup (i.e., 0–10 years, 10–20 years, or 21–30 years).[86]

ST segment or T wave abnormalities. Eight studies evaluated the presence of either ST segment (defined by various combinations of Minnesota codes 4.1, 4.2, 4.3, or 4.4) or T wave abnormalities (defined by various combinations of Minnesota codes 5.1, 5.2, 5.3, or 5.4) (**Table 3**).[70,74-76,84,85,92,93] One study evaluated CVD death[74] and one study evaluated incident CHF[75] (the latter was excluded from the meta-analysis). Five studies restricted enrollment to male subjects.[70,84,92,93] In the other four studies, the proportion of male subjects ranged from 40 to 55 percent.[74-76,85] Duration of followup ranged from 3 to 29 years and incidence of CHD or CVD death ranged from 0.3 to 21 percent.

After adjustment for traditional cardiac risk factors, the pooled hazard ratio for ST segment or T wave abnormalities, with regard to subsequent cardiovascular events, was 1.9 (95% CI, 1.6 to 2.4; I^2=50 percent) (**Figure 2**).[70,74,76,84,85,92,93] Although statistical heterogeneity was moderate, all of the studies found a statistically significant association (HR point estimates ranged from 1.5 to 3.8). Excluding the one study[74] that evaluated CVD death instead of CHD death did not reduce the statistical heterogeneity and resulted in an unchanged pooled estimate (HR, 1.9 [95% CI, 1.6 to 2.3]; I^2=45 percent). Only one study was rated as good quality (the others were rated as fair quality); the estimate from this study was similar to the pooled estimate (HR, 2.1 [95% CI, 1.4 to 3.2]).[93] Meta-regression analyses showed that restriction of enrollment to male subjects (p=0.24) and variability in duration of followup (p=0.24) or number of traditional risk factors adjusted for (p=0.84) did not explain the between-study variance in hazard ratio estimates. One study that was excluded from the meta-analysis found an association between ST segment or T wave abnormalities and incident CHF (HR, 1.6 [95% CI, 1.3 to 2.l]).[75]

Left ventricular hypertrophy. Ten studies evaluated LVH on resting ECG as a predictor of various cardiovascular outcomes (**Table 4**).[66,67,71,79,80,82,84,86,87,93] Six studies defined LVH based on Minnesota codes for high voltage plus ST segment or T wave abnormalities,[67,71,79,80,84,86] one used the Cornell voltage criteria,[82] one used the Romhilt and Estes criteria,[93] one evaluated various criteria for new or increased LVH on 6-year followup ECG (this study was excluded from the meta-analysis),[87] and one did not state how LVH was defined.[66] Two studies evaluated CVD death,[79,80] one evaluated nonfatal MI or CHD death,[82] one focused on stroke (this study was excluded from the meta-analysis),[86] and the remainder evaluated CHD death. Five studies restricted enrollment to male subjects.[66,84,86,87,93] In the other five studies, the proportion of male subjects ranged from 35 to 52 percent. Duration of followup ranged from 10 to 21 years and

incidence of CHD or CVD death ranged from 0.6 to 9 percent.

After adjustment for traditional risk factors, the pooled hazard ratio for LVH, with regard to subsequent cardiovascular events, was 1.6 (8 studies [95% CI, 1.3 to 2.0]; I^2=46 percent) (**Figure 3**).[66,67,71,79,80,82,84,93] Statistical heterogeneity appeared to be completely explained by inclusion of the lone study that did not find an increased risk or trend toward increased risk of cardiovascular events (HR, 0.85 [95% CI, 0.55 to 1.3]).[66] Although statistical heterogeneity was no longer present after this study was excluded, the pooled estimate only changed slightly (HR, 1.7 [95% CI, 1.4 to 2.1]; I^2=0 percent). It was not clear why this study was an outlier. Other than not describing how LVH was defined, it met criteria for a good-quality study. One study excluded from the meta-analysis found that increased LVH on 6-year followup ECG compared with baseline was associated with increased risk of CHD death,[87] and another study excluded from the meta-analysis found no association between presence of LVH and subsequent stroke (estimates not reported).[86]

Pooled estimates were similar when studies were stratified according to whether LVH was defined based on Minnesota code criteria (5 studies; HR, 1.7 [95% CI, 1.4 to 2.0]; I^2=0 percent) [67,71,79,80,84] or other criteria (3 studies; HR, 1.4 [95% CI, 0.77 to 2.5]; I^2=46 percent),[66,82,93] or according to whether they evaluated CHD death (5 studies; HR, 1.5 [95% CI, 0.99 to 2.1]; I^2=48 percent)[67,71,79,80,84] or another cardiovascular outcome (3 studies; HR, 1.8 [95% CI, 1.3 to 2.4]; I^2=47 percent).[79,80,82] Estimates were lower in studies rated as good quality (4 studies; HR, 1.2 [95% CI, 0.90 to 1.7]; I^2=31 percent)[66,71,80,93] compared with those rated as fair quality (4 studies; HR, 2.0 [95% CI, 1.6 to 2.5]; I^2=0 percent) (p=0.03 for difference).[67,79,82,84] Meta-regression analyses showed that the proportion of male enrollees (p=0.13), the duration of followup (p=0.06), and the number of traditional risk factors adjusted for (p=0.74) did not explain the between-study variance in hazard ratio estimates.

Left axis deviation and bundle branch block. Three studies[71,84,93] evaluated left axis deviation (**Table 4**) and five studies[71,73,82,84,85] evaluated bundle branch block (**Table 4**) on resting ECG as predictors of cardiovascular outcomes. One study defined bundle branch block as incomplete or complete based on QRS duration and evaluated CHF incidence.[73] All of the other studies defined ECG abnormalities using Minnesota code criteria; of these, all except for one evaluated CHD death. The exception was a study that evaluated the association between bundle branch block and the combination of nonfatal MI or CHD death.[82]

For left axis deviation, the pooled hazard ratio, after adjusting for traditional risk factors, was 1.5 (3 studies [95% CI, 1.1 to 1.9]; I^2=0 percent) (**Figure 3**).[71,84,93]

For bundle branch block, the pooled hazard ratio, after adjusting for traditional risk factors, was also 1.5 (4 studies [95% CI, 0.98 to 2.3]; I^2=46 percent), although results were not statistically significant, in part due to greater statistical heterogeneity and less precise estimates (**Figure 3**).[71, 82,84,85] One study not included in the meta-analysis found something of a dose-response, in that incomplete (QRS, 100–119 ms; HR, 1.4 [95% CI, 1.0 to 2.0]) and complete bundle branch block (QRS ≥120 ms; HR, 1.7 [95% CI, 1.3 to 2.4]) were associated with an increased risk of CHF compared with no bundle branch block at a mean followup of 12.7 years.[73]

Major and minor ECG abnormalities. Six studies evaluated the association between presence of major or minor resting ECG abnormalities and subsequent cardiovascular events (**Table 5**).[71,72,77,81,84,93] Because definitions for major and minor abnormalities varied widely between studies, we did not pool results. Two studies reported an association between presence of a major abnormality on resting ECG and CHD death through 10 years (HR, 2.3 [95% CI, 1.5 to 3.7][71] and HR, 3.1 [95% CI, 1.9 to 5.1][84]), and a third study reported an association with CHD events through 5 years (HR, 3.0 [95% CI, 2.0 to 4.5]).[72]

Six studies also evaluated the association between minor abnormalities on resting ECG and subsequent cardiovascular events.[71,72,77,81,84,93] From a given study, risk estimates for minor abnormalities were weaker than estimates for major abnormalities, suggesting a potential dose effect. For example, one study reported a hazard ratio of 1.8 (95% CI, 1.3 to 2.5) for minor abnormalities and subsequent CHD death compared with a hazard ratio of 3.1 (95% CI, 1.9 to 5.1) for major abnormalities.[84] In some cases, the association between minor abnormalities and subsequent CHD events did not reach statistical significance.[71,93]

Other resting ECG abnormalities. Other resting ECG abnormalities have been evaluated, including prolonged QT interval, ischemic changes, atrial fibrillation, right axis deviation, presence of Q waves, ventricular premature contractions, high resting heart rate, and others (**Table 6**).[68,75,77,78,82,83,85,89-91,130] Two studies found that ischemic changes on resting ECG (defined using different Minnesota code criteria) was associated with increased risk of subsequent CHD death after 10 years of followup (HR, 1.7 [95% CI, 1.1 to 1.7][71] and HR, 1.5 [95% CI, 1.1 to 2.1][84]), after adjustment for traditional risk factors (**Table 7**). Two other studies reported inconsistent results for the association between prolonged QT interval on resting ECG and subsequent cardiovascular events, but varied in how they defined QT prolongation, the outcomes assessed, and duration of followup (**Table 8**).[82,90] Other ECG abnormalities were evaluated in only one study or too variably defined across studies to draw firm conclusions about their usefulness as predictors.

Stratification by sex. In studies that stratified results by sex, estimates of risk associated with various resting ECG abnormalities in men and women were similar, or had overlapping confidence intervals (**Table 9**).

Evidence: Exercise ECG

Thirty-eight prospective cohort studies of exercise ECG met inclusion criteria (**Table 10**).[66,78,94-129] Six studies reported results from the Kuopio Ischemic Heart Disease Risk Factor Study,[108,109,111-113,126] three from MRFIT,[94,120,122] two from the St. James Women Take Heart Study,[104,105] four from the Baltimore Longitudinal Study of Aging,[101,106,124,125] three from the Framingham Offspring Study,[110,118,119] three from the Lipid Research Clinics Prevalence Study,[98,116,117] two from the Lipid Research Clinics Coronary Primary Prevention Trial,[100,127] two from the Paris Protective Study I,[78,107] and two from the Aerobics Center Longitudinal Study.[97,129] Excluding double-counted populations, the studies evaluated a total of 91,746 subjects. Duration of followup ranged from 2.8[123] to 25 years.[94]

Nineteen studies were rated as good quality,[66,78,94,96,98-102,104,107,111-113,116,119,122,124,127] and the

remainder as fair quality (**Appendix C2**). The most common methodological shortcomings were failure to describe how patients with uninterpretable ECG results were handled (25/38 studies), failure to describe loss to followup (22/38), and failure to describe race when reporting baseline demographic characteristics (24/38). Three studies[114,115,123] only enrolled persons with diabetes mellitus or impaired fasting glucose and are reviewed separately.

Reclassification, calibration, and discrimination. No study estimated how accurately exercise ECG plus traditional risk factor assessment classified subjects into high-, intermediate-, or low-risk groups compared with classification based on traditional risk factor assessment alone, or provided data to enable construction of risk stratification tables. One study evaluated risks associated with abnormalities on exercise ECG in subjects stratified into low, intermediate, or high 10-year predicted-risk groups based on traditional risk factors.[96] It found that ST segment depression was associated with a slight trend toward progressively weaker risk estimates with lower baseline risk (HR, 2.1 [95% CI, 1.1 to 4.2]; HR, 2.0 [95% CI, 1.0 to 4.0]; and HR, 1.6 [95% CI, 0.56 to 4.3] for high-, intermediate-, and low-risk groups, respectively), but confidence intervals were wide and overlapping. For failure to reach target heart rate, the trend was somewhat more pronounced, but estimates also overlapped (HR, 2.7 [95% CI, 1.5 to 4.7]; HR, 1.7 [95% CI, 0.96 to 3.0]; and HR, 0.74 [95% CI, 0.23 to 2.4]).

One study found a C statistic of 0.73 (confidence intervals not reported) for traditional risk factor assessment using the European Systematic Coronary Risk Evaluation (SCORE) alone compared with 0.76 for SCORE plus exercise ECG variables (including number of metabolic equivalents [METs], peak heart rate, impaired functional capacity, heart rate recovery, ventricular ectopy, and ischemic ST segment changes).[95] SCORE was used instead of Framingham risk factor assessment because the latter was associated with a C statistic of 0.57. One other study reported a similar C statistic when comparing a model with the Duke treadmill score to one with the number of METs achieved during exercise, with both controlling for Framingham risk score.[104] However, the study did not report the C statistic for the Framingham risk score without exercise ECG findings.

Adjusted risk estimates.

ST depression with exercise. Twenty-one studies evaluated the association between ST depression with exercise and subsequent cardiovascular events (**Table 11**).[66,95,96,99-103,106-109,111,113,116,120,122,124-127] Estimates were pooled from 12 of the 20 studies.[66,95,96,99,100,102,103,107,113,116,120,125] One study was not included in the meta-analysis because it focused on stroke as an outcome.[109] Eight other studies[101,106,108,111,122,124,126,127] were excluded because other studies of the same population[100,113,120,125,126] also evaluated ST depression and either reported longer duration followup, a preferred outcome (CHD or CVD death), or defined ST segment depression more like the other studies in the meta-analysis.

Among the studies included in the meta-analysis, four studies[66,120,124,126] defined abnormal ST segment depression with exercise as $\geq$0.5 mm and the rest defined abnormal ST segment depression as $\geq$1.0 mm. Three studies evaluated CHD death,[66,100,120] four evaluated CVD death,[103,107,113,116] one evaluated all-cause mortality,[95] and four evaluated a composite cardiovascular outcome (various combinations of angina, MI, sudden cardiac death, and CHD

death).[96,99,102,125] Six studies restricted enrollment to men[66,100,103,107,113,120] and one study restricted enrollment to women.[116] In the remaining studies, the proportion of male subjects ranged from 47 to 81 percent. Duration of followup ranged from 6 to 23 years and the incidence of cardiovascular events ranged from 2 to 15 percent.

After adjusting for traditional cardiac risk factors, the pooled hazard ratio for ST depression with exercise and subsequent cardiovascular events was 2.1 (95% CI, 1.6 to 2.9) (**Figure 4**).[66,95,96,99,100,102,103,107,113,116,120,125] Although heterogeneity was present (I^2=71 percent), all of the studies except for two found at least a trend toward an association between exercise-induced ST segment depression and subsequent cardiovascular events. One exception was a study that differed from the others in the meta-analysis because it only enrolled women (HR, 0.88 [95% CI, 0.48 to 1.6]).[116] However, exclusion of this study from the meta-analysis resulted in a similar estimate (HR, 2.3 [95% CI, 1.7 to 3.1]) and did not decrease the heterogeneity (I^2=68 percent). Another exception (HR, 1.0 [95% CI, 0.57 to 1.9]) was a study that only reported all-cause mortality and controlled for traditional risk factors using the SCORE instrument, which it found performed better than the Framingham risk score.[95] Excluding this study also resulted in a similar estimate (HR, 2.3 [95% CI, 1.7 to 3.1]) and did not decrease the heterogeneity (I^2=70 percent). Statistical heterogeneity was not reduced and estimates were similar when studies were stratified according to whether they used a treadmill for exercise (7 studies; HR, 2.0 [95% CI, 1.3 to 3.2]; I^2=76 percent)[95,96,100,103,116,120,125] or a bicycle (3 studies; HR, 2.0 [95% CI, 1.3 to 3.0]; I^2=83 percent),[66,107,113] whether they evaluated CHD death (3 studies; HR, 2.2 [95% CI, 0.94 to 5.2]; I^2=82 percent),[66,100,120] CVD death (4 studies; HR, 2.1 [95% CI, 1.2 to 3.7]; I^2=77 percent),[103,107,113,116] or a composite cardiovascular outcome (4 studies; HR, 2.6 [95% CI, 1.8 to 3.8]; I^2=43 percent),[96,99,102,125] or whether they were rated as good quality (9 studies; HR, 2.2 [95% CI, 1.6 to 3.1]; I^2=72 percent)[66,96,99,100,102,107,113,116,125] or fair quality (3 studies; HR, 1.8 [95% CI, 0.7 to 4.4]; I^2=77 percent).[95,103,120] In meta-regression analyses, the degree of ST depression deemed abnormal (i.e., >0.5 mm vs. >1 mm) (p=0.53), the proportion of male enrollees (p=0.18), the number of risk factors adjusted for (p=0.52), and the duration of followup (p=0.36) did not explain the between-study variance in hazard ratio estimates.

Chronotropic incompetence. Seven studies evaluated chronotropic incompetence during exercise (**Table 12**, **Figure 5**).[66,78,94,96,110,116,128] Four studies evaluated failure to achieve target heart rate (either 85 or 90 percent of maximum predicted heart rate) as a dichotomous variable.[94,96,110,116] Of these studies, one study evaluated CVD death,[116] one CHD death,[94] and two various CHD events.[110,116] After adjusting for traditional cardiovascular risk factors, the pooled hazard ratio for failure to reach target heart rate and subsequent cardiovascular events was 1.4 (95% CI, 1.3 to 1.6; I^2=0 percent).[94,96,110,116] Two other studies that evaluated chronotropic response as a multicategory variable found that the lowest category was associated with increased risk of cardiovascular events or all-cause mortality compared with the highest category.[78,128] One other study evaluated maximum heart rate achieved during exercise as a continuous variable.[66] It found that increased maximum heart rate was associated with decreased risk of CHD death (relative risk [RR], 0.75 per 13.3 beats/min [SD, 1] [95% CI, 0.66 to 0.8]).

Heart rate recovery. Four studies evaluated abnormal heart rate recovery after exercise as a predictor of cardiovascular events or all-cause mortality (**Table 12**, **Figure 5**).[78,95,98,118] The trials varied in how they defined abnormal heart recovery (decrease of 12 or 25 beats/min from peak

heart rate 1 minute into recovery, decrease of <42 beats/min after 2 minutes, or assessed as a continuous variable), and one study[118] showed no association between abnormal heart rate recovery, based on several definitions, and cardiovascular outcomes or all-cause mortality after adjustment for traditional risk factors (HR, 1.2 [95% CI, 0.71 to 2.1] for abnormal heart rate recovery at 1 minute). Nonetheless, the pooled hazard ratio for abnormal heart rate recovery and all-cause mortality, based on three trials, was 1.5 (95% CI, 1.3 to 1.9), with no statistical heterogeneity (I^2=0 percent). Cardiovascular-specific outcomes were not reported consistently across the trials and could not be pooled. The fourth trial could not be pooled because it did not analyze heart rate recovery as a dichotomous variable, but it found that recovery at 1 minute of <25 beats/min was associated with increased risk of all-cause mortality compared with heart rate recovery of >40 beats/min.[78]

Ventricular ectopy. Two studies found that ventricular ectopy during or after exercise ECG was associated with subsequent cardiovascular events (**Table 12**).[107,116] In one study, having ≥2 consecutive premature ventricular depolarizations or frequent (>10 percent) ventricular depolarizations was associated with a hazard ratio of 2.5 (95% CI, 1.6 to 3.9) for cardiovascular death.[107] In the other study, presence of multifocal or frequent premature ventricular depolarizations or termination of the test due to ventricular tachyarrhythmia was associated with increased risk of CVD death (HR, 1.7 [95% CI, 1.1 to 2.6]) and all-cause mortality (HR, 1.2 [95% CI, 0.90 to 1.6]).[116]

Exercise capacity or fitness level. Nine studies evaluated exercise capacity or fitness based on exercise ECG (**Table 13**).[95,97,104,105,113,121,125,126,129] In each of the studies, increased exercise capacity or fitness was consistently associated with decreased risk of cardiovascular events or all-cause mortality. Results could not be pooled because the studies evaluated different markers of exercise capacity or fitness and analyzed them differently (as continuous, dichotomous, or multiple category variables). In two reports from the same study of women, lower METs achieved during exercise predicted CHD death when analyzed as a categorical variable (HR, 3.1 for <5 METs vs. >8 METs [95% CI, 2.1 to 4.8] and HR, 1.9 for 5–8 METs vs. >8 METs [95% CI, 1.3 to 2.9])[105] or as a continuous variable (HR, 0.83 per 1 MET increase [95% CI, 0.78 to 0.89]).[104] One study of men found that lower exercise capacity (based on highest workload during exercise) was associated with increased risk of CVD death and all-cause mortality when the lowest quartile (<162 W) was compared with the highest quartile (HR, 2.0 for CVD death [95% CI, 1.1 to 3.6] and HR, 2.5 for all-cause mortality [95% CI, 1.7 to 3.7]) or as a continuous variable (per 20 W increment; HR, 0.86 for CVD death [95% CI, 0.79 to 0.93] and HR, 0.85 for all-cause mortality [95% CI, 0.80 to 0.89]).[113] Another study found that the number of METs predicted all-cause mortality when evaluated as a dichotomous variable (<9.5 METs for men or <7.5 for women vs. higher number of METs; HR, 3.0 [95% CI, 2.0 to 4.4]) after adjusting for traditional risk factors, or as a continuous variable (HR, 1.3 per 1 MET decrease [95% CI, 1.2 to 1.4]) after adjusting for traditional risk factors and exercise ECG variables.[95] One study found that high fitness (defined as exercise time in the upper 2 quintiles) was associated with reduced risk of CVD events (MI, revascularization, or stroke) compared with low fitness (lowest quintile) in men (HR, 0.75 [95% CI, 0.64 to 0.87]).[129] The estimate was similar in women, but did not reach statistical significance (HR, 0.78 [95% CI, 0.49 to 1.2]). An earlier report from the same study reported consistent results when subjects were categorized into two rather than three fitness levels (HR, 1.7 [95% CI, 1.3 to 2.2] for men and HR, 2.1 [95% CI, 1.4 to 3.3] for

women).[97] One study found that low work capacity (defined as <age-based median) was associated with increased risk of fatal or nonfatal MI (RR, 2.2 [95% CI, 1.1 to 4.7]).[121] Two other studies evaluated continuous measures of exercise capacity. One study found that increased duration of exercise was associated with decreased risk of coronary events (HR, 0.87 beats/min [95% CI, 0.79 to 0.96]).[125] Estimates were similar in women but did not reach statistical significance. The other study found that lower workload achieved at a heart rate of 100 beats/min was associated with increased risk of CHD death (HR, 1.9 per decrement of 31 W [95% CI, 1.3 to 2.8]).[126]

Other abnormalities on exercise ECG. Three studies evaluated other abnormalities, or combinations of abnormalities, on exercise ECG as predictors of subsequent cardiovascular events (**Table 14**).[97,104,117,131] One study found that decreased peak oxygen pulse (defined as maximal oxygen uptake/peak heart rate) was associated with increased risk of CHD death (HR, 2.4 [95% CI, 1.1 to 5.4] for peak oxygen pulse <13.5 ml/beat vs. >17.8 ml/beat) and all-cause mortality (HR, 1.8 [95% CI, 1.2 to 2.6]).[97] One study found that a Duke treadmill score (defined as exercise time – [5 x ST deviation] – [4 x angina score index]) <5 was associated with increased risk of CHD death (HR, 2.7 [95% CI, 1.6 to 4.8]) and all-cause mortality (HR, 2.2 [95% CI, 1.6 to 3.1]).[104] The third study found that abnormal exercise ECG was associated with increased risk of CVD death and all-cause mortality, but did not define "abnormal."[97] One study found that presence of both low heart rate recovery and low METs (categorized as "low" or "high" based on sex-specific medians) was a stronger predictor of CVD death at 20 years than presence of either low heart rate recovery or low METs alone (vs. high heart rate recovery and high METs; HR for low heart rate recovery or low METs, 1.5 [95% CI, 0.83 to 2.7] for men and 3.1 [95% CI, 1.3 to 7.4] for women; HR for low heart rate recovery and low METs, 3.5 [95% CI, 2.0 to 6.2] for men and 8.3 [95% CI, 3.6 to 20]) for women.[117]

Stratification by sex. In studies that stratified results by sex, estimates of risk associated with various exercise ECG abnormalities in men and women were similar, or had overlapping confidence intervals (**Table 15**).

Studies of patients with diabetes. Two studies evaluated exercise ECG in persons with diabetes (**Table 16**).[114,123] One study found that 1 mm of ST segment depression or elevation with exercise was associated with an increased risk of CHD death (HR, 2.1 [95% CI, 1.3 to 3.3]) after adjustment for traditional risk factors that was comparable to the risk observed in studies of persons without diabetes.[114] The second study also found that exercise-induced ST depression was associated with increased risk of any CHD event (cardiac death, MI, or new-onset angina), but the sample size was small (n=86) and confidence intervals were very imprecise (HR, 21 [95% CI, 2 to 204]).[123]

One other study evaluated exercise ECG in women with impaired fasting glucose (100 to 125.9 mg/dL) or undiagnosed diabetes (fasting glucose $\geq$126 mg/dL, no history of diabetes, and not taking hypoglycemia medication). It found that moderate or high fitness (based on age-specific maximal exercise duration and oxygen uptake in METs) was associated with decreased risk of all-cause mortality compared with low fitness (HR, ~0.65 for either moderate or high fitness).[115]

Key Question 4. What Are the Harms of Screening With Resting or Exercise Electrocardiography?

Summary

We identified no studies that reported harms directly associated with screening with resting ECG, though direct harms are likely to be minimal. One study reported no complications in 377 subjects who underwent exercise ECG. Evidence from populations that included symptomatic persons suggests that harms associated with exercise ECG are likely to be small.

No study evaluated harms associated with followup testing or interventions following resting or exercise ECG. Studies that reported rates of angiography and revascularization procedures following screening with exercise ECG did not meet formal inclusion criteria because they did not report harms associated with these interventions or compare results between screened and unscreened persons. However, such studies might provide some information about potential downstream harms based on known complications associated with these procedures. In 10 studies, the proportion of patients who underwent angiography following screening with exercise ECG ranged from 0.6 to 1.7 percent, after excluding an outlier study. In two studies, 0.5 percent or fewer of patients who underwent screening with exercise ECG subsequently underwent a revascularization procedure. No study evaluated harms associated with use of lipid-lowering therapy or aspirin to reduce cardiovascular risk following screening.

Evidence

Direct harms. Because resting ECG is noninvasive and does not involve exercise, direct harms are likely to be minimal, but could include anxiety about the test or labeling effects. However, we identified no studies that reported harms directly associated with screening with resting ECG. For exercise ECG, potential direct harms include cardiovascular events associated with exercise, injuries associated with exercise, anxiety about the test, and labeling. One study included in the previous USPSTF review reported no complications in the study population (n=377) as a direct result of screening with exercise ECG.[132] Based on survey data that included symptomatic patients, serious adverse events occurring as a result of exercise ECG, including arrhythmia (<0.2 percent), acute MI (0.04 percent), or sudden cardiac death (0.01 percent), are rare. The overall risk of experiencing either an event that requires hospitalization or sudden death has been estimated to be 1 per 10,000 tests.[133]

Harms associated with subsequent tests or interventions. Screening with resting or exercise ECG could also result in harms related to subsequent tests or interventions. Some patients with abnormalities on resting or exercise ECG might undergo further evaluation for presence of CHD, including use of exercise echocardiography, myocardial perfusion imaging, angiography, or CT angiography. Subsequent interventions might be related to use of lipid-lowering therapy, aspirin, or revascularization procedures.

We identified no studies on harms associated with followup testing or interventions after screening with resting or exercise ECG. We identified 11 studies that reported rates of

angiography or revascularization procedures following screening with exercise ECG in asymptomatic persons.[95,99,132,134-141] Although these studies did not directly measure harms associated with angiography or revascularization procedures and therefore do not meet formal inclusion criteria, they are discussed here because it might be possible to estimate harms based on the known rates of complications associated with these interventions.

Nine studies[132, 34-141] reporting angiography rates were summarized in the previous USPSTF evidence review.[8] In these studies, rates of subsequent angiography in primarily asymptomatic patients following an abnormal exercise ECG ranged from 0.6 to 13 percent. One outlier study (13 percent angiography rate)[139] evaluated a cohort of veterans with hypertension. Exclusion of this study narrowed the range of observed angiography rates (0.6 to 2.9 percent). Two studies published since the previous USPSTF review (n=4605) reported rates of angiography following screening with exercise ECG as part of a routine, executive physical examination (**Table 17**).[95,99] In these two studies, 8.5 and 10 percent of subjects had an abnormal ST segment response to exercise, and 0.6 and 1.7 percent of the total sample (or within the range from the studies included in the prior USPSTF review) underwent angiography following exercise ECG.[95,99] Based on total study samples, 0.1 percent (4/3554) and 0.5 percent (5/1051) underwent a revascularization procedure (coronary artery bypass surgery or a percutaneous coronary intervention) following exercise ECG.[95,99]

None of the studies described above estimated complications associated with angiography or revascularization procedures. Based on large, population-based registries, the risk of having any serious adverse event as a result of angiography is 1.7 percent; this includes risk of death (0.1 percent), MI (0.05 percent), stroke (0.07 percent), and arrhythmia (0.4 percent).[142]

Coronary angiography, CT angiography, and myocardial perfusion imaging are associated with radiation exposure that could increase cancer risk. Coronary angiography is associated with an average effective radiation dose of 7 mSv, accounting for an estimated 5 percent of the total effective dose from all medical imaging procedures.[143] Myocardial perfusion imaging is associated with an average radiation dose of 15.6 mSv, accounting for 22 percent of the dose from all medical imaging procedures.[143]

Patients who have an abnormal screening test and undergo additional testing, but do not have coronary artery disease, are subjected to potential harms without the possibility of benefit. Understanding the false-positive rate for coronary artery disease among persons with abnormalities on resting or exercise ECG could help inform judgments regarding the balance of benefits and harms for screening. However, data on the prevalence of coronary artery disease among persons who underwent coronary angiography as a result of screening ECG (resting or exercise) are limited. One study included in the prior USPSTF review found "severe" coronary artery disease in 15 percent of patients who underwent angiography.[141] Another study included in the prior USPSTF review found that 55 percent of patients who underwent angiography had at least 50 percent occlusion in at least one coronary artery, and 37 percent had at least 70 percent occlusion in at least one coronary artery.[134] A recent, large (nearly 400,000 patients) study that evaluated a primarily symptomatic (70 percent) population who underwent angiography found that 39 percent of patients had no coronary artery disease (defined as <20 percent stenosis).[144]

Abnormal findings on resting or exercise ECG could also result in harms associated with increased use of treatments for reducing cardiovascular risk. We identified no studies that assessed harms associated with lipid-lowering therapy or aspirin following ECG screening. General harms associated with lipid-lowering therapy or aspirin for primary prevention of cardiovascular events have been reviewed in other USPSTF reports.[33,34]

Chapter 4. Discussion

Summary of Review Findings

The results of the evidence review are summarized in **Table 18**. As in previous USPSTF reviews, we found no studies that evaluated clinical outcomes associated with screening with resting or exercise ECG compared with no screening. We also found no studies on how screening affects use of therapies to reduce cardiovascular risk (lipid-lowering therapy or aspirin). Another critical research gap is that no studies directly evaluated the incremental value of screening ECG when added to traditional risk assessment for accurately classifying patients into different risk categories.

The lack of information on reclassification is critical from a clinical perspective, since treatment decisions regarding therapies for reducing cardiovascular risk are often based on whether a patient is classified as low- (<10 percent risk over the next 10 years), intermediate- (10 to 20 percent risk), or high-risk (>20 percent risk) for future CHD events. From the information currently available, it is not possible to determine the degree to which performing resting or exercise ECG in an individual patient more accurately moves them from one risk category to another versus yielding a more precise estimate within the same risk category, which is less clinically useful. For example, in populations at very low risk (<5 percent) for CHD events, such as most young adults, even a doubling of risk is unlikely to move an individual from a low-risk to a higher-risk category. Similarly, in persons already at high risk based on traditional risk factor assessment, abnormalities on resting or exercise ECG are unlikely to change management decisions. The greatest potential benefits of screening with resting or exercise ECG are likely to be in intermediate-risk patients, since the presence of abnormalities could shift persons into the high-risk group, where additional interventions might be warranted, but no study reported how many persons classified as intermediate risk based on traditional risk factor assessment would be reclassified as high risk following screening. Two studies evaluated effects on the C statistic of adding resting or exercise ECG findings to traditional risk factor assessment compared with traditional risk factor assessment alone,[72,95] but this measure is of limited clinical usefulness because it does not provide information about the actual predicted risks in an individual patient, or the proportion of patients classified (or reclassified) as high, intermediate, or low risk.[57] Both showed slight improvements in the C statistic, though the difference did not appear statistically significant in one study,[72] and confidence intervals for the estimates were not reported in the other.[95]

The bulk of the available evidence came from over 60 studies of more than 250,000 subjects that evaluated whether abnormalities on resting or exercise ECG are associated with an increased risk of subsequent cardiovascular events. Unlike previous USPSTF reviews, we focused on studies that adjusted for at least five of the seven Framingham risk factors, in order to better understand the incremental value of adding resting or exercise ECG for predicting cardiovascular events. Based on pooled analyses, a number of abnormalities on resting (ST segment abnormalities, T wave abnormalities, LVH, left axis deviation, bundle branch block) or exercise (ST segment depression with exercise, failure to reach target heart rate) ECG were associated with an increased risk of subsequent cardiovascular events. The magnitude of increased risk ranged from

an adjusted pooled hazard ratio of around 1.4 to around 2.1 for either resting or exercise ECG abnormalities (**Table 1**). An exception was variously defined "major" resting ECG abnormalities, which were associated with somewhat greater hazard ratios (range, 2.3 to 3.7) than those observed for "minor" resting ECG abnormalities (range, 1.1 to 2.1) (**Table 5**). Although statistical heterogeneity was present in most analyses, the point estimates from almost all studies favored an association, estimates were stable in stratified analyses (based on study quality, method of defining the ECG abnormality, and cardiovascular outcome assessment), and meta-regression analyses (based on differential duration of followup, proportion of male subjects, and number of Framingham risk factors adjusted for) did not explain the between-study variance. Low versus high exercise capacity or fitness during exercise ECG was also associated with increased risk of subsequent cardiovascular events or all-cause mortality, with hazard ratios ranging from 1.7 to 3.1, but data could not be pooled. Despite the strong evidence that abnormalities on resting or exercise ECG are associated with an increased risk of subsequent cardiovascular events beyond the risk accounted for by assessment of traditional risk factors, information on the diagnostic usefulness of these tests is incomplete, since understanding the usefulness of screening requires additional information on reclassification and whether reclassification leads to clinical actions that improve patient outcomes.[16]

Evidence on harms associated with screening using resting or exercise ECG is limited. Nonetheless, serious direct harms appear to be minimal with resting ECG (other than possibly anxiety or labeling) and small or rare with exercise ECG (ischemia associated with exercise, injuries related to exercise), assuming appropriate attention to absolute and relative contraindications to exercise testing and adherence to standard safety precautions for terminating a test. Perhaps of greater concern than the direct harms associated with the test itself are the downstream harms that could result from additional testing or interventions as a result of screening. For example, some patients undergo angiography following screening ECG, and are therefore exposed to the potential harms related to that procedure, including bleeding, radiation exposure, and contrast allergy or nephropathy. Similarly, patients who are placed on lipid-lowering therapy or aspirin as a result of ECG screening are exposed to the harms related to those interventions. Evidence on downstream harms associated with screening is not available, with data primarily limited to rates of patients who subsequently undergo angiography (range, 0.6 to 1.7 percent). A small proportion (<1 percent) of patients undergo revascularization with coronary artery bypass graft surgery or a percutaneous coronary intervention following screening with exercise ECG, despite the lack of evidence on benefits associated with these interventions in asymptomatic persons and the known risks associated with those procedures.[95,99]

Limitations

We only included English-language studies, which could result in language bias. Studies that evaluated the risk associated with various resting or exercise ECG abnormalities varied in quality and duration of followup, assessed different cardiovascular outcomes, and used different methods to define the abnormalities. We therefore used a random effects model to perform meta-analysis. Although statistical heterogeneity was present in several of the meta-analyses, stratified analyses and meta-regression had little impact on estimates and conclusions. Referral bias could have resulted in underestimates of the risk associated with ECG abnormalities if their identification led to increased use of treatments effective at reducing cardiovascular risk.

Emerging Issues/Next Steps

Resting and exercise ECG are technologies that have been available for many years. Most of the studies included in this review evaluated the usefulness of long-established and widely recognized abnormalities on resting or exercise ECG for predicting future cardiovascular events. However, newer abnormalities (or refinements of established abnormalities) on resting (such as the QRS/T angle, high QRS nondipolar voltage, and decreased heart rate variability)[90,91] or exercise ECG (such as heart rate adjustment of ST depression, QT interval and T wave subintervals, and heart rate recovery)[145] have been proposed as potentially better predictors of cardiovascular events, and may warrant further study.

Future Research

Studies that directly evaluate how screening with resting or exercise ECG affects clinical outcomes compared with not screening, or how screening affects use of interventions to reduce cardiovascular risk, are needed. Any study of screening should also evaluate harms associated with screening, as well as downstream harms related to additional testing and therapies. Although randomized trials would be desirable, well-conducted prospective studies with adequate sample sizes and sufficient duration of followup could also be informative.

In lieu of direct evidence on the clinical effects of screening, future studies on risk prediction should provide data to enable estimates of reclassification, from which potential benefits of screening might be extrapolated, based on the known efficacy of interventions in high-risk populations. Decisions to allocate resources to update this or similar reviews on the usefulness of ECG screening might be predicated on the availability of such evidence that can be identified using literature scans or other methods. Many of the studies included in this review evaluated large sample sizes over long periods of time, and the information needed to assess reclassification rates in these databases likely already exists. Therefore, a more efficient method than initiating new studies for obtaining information on reclassification would be to reanalyze preexisting databases.

Some studies suggest that the association between abnormalities on resting or exercise ECG and subsequent cardiovascular events might vary in subpopulations defined by race[82] or sex.[76,116] Research is needed to better understand whether and how the usefulness of different ECG abnormalities as predictors varies in different subpopulations, in order to inform optimal screening strategies. From a comparative effectiveness perspective, studies that evaluate newer compared with more traditional abnormalities on resting or exercise ECG would be valuable, as would be studies that evaluate the usefulness of combinations of ECG abnormalities compared with single findings, and studies that compare screening with resting or exercise ECG versus cardiac CT, carotid artery intima-media thickness ultrasonography, or other imaging modalities.

Conclusions

There is no direct evidence on benefits of screening with resting or exercise ECG on clinical

outcomes, and no evidence on how screening affects use of therapies to reduce cardiovascular risk. There is strong evidence that abnormalities on resting or exercise ECG are associated with mildly increased risk of subsequent cardiovascular events after adjusting for traditional cardiovascular risk factors. Estimates of increased risk were similar for resting and exercise ECG abnormalities. The clinical implications of these findings are unknown, as pooled risk estimates do not necessarily indicate the degree to which resting or exercise ECG results in accurate reclassification of persons into CHD risk categories or has an impact on clinical decisions and subsequent patient outcomes. Evidence on harms associated with screening is limited. Although direct harms associated with screening appear to be small, downstream harms related to subsequent testing and interventions are likely to be an important factor in assessing the balance of benefits and harms associated with screening.

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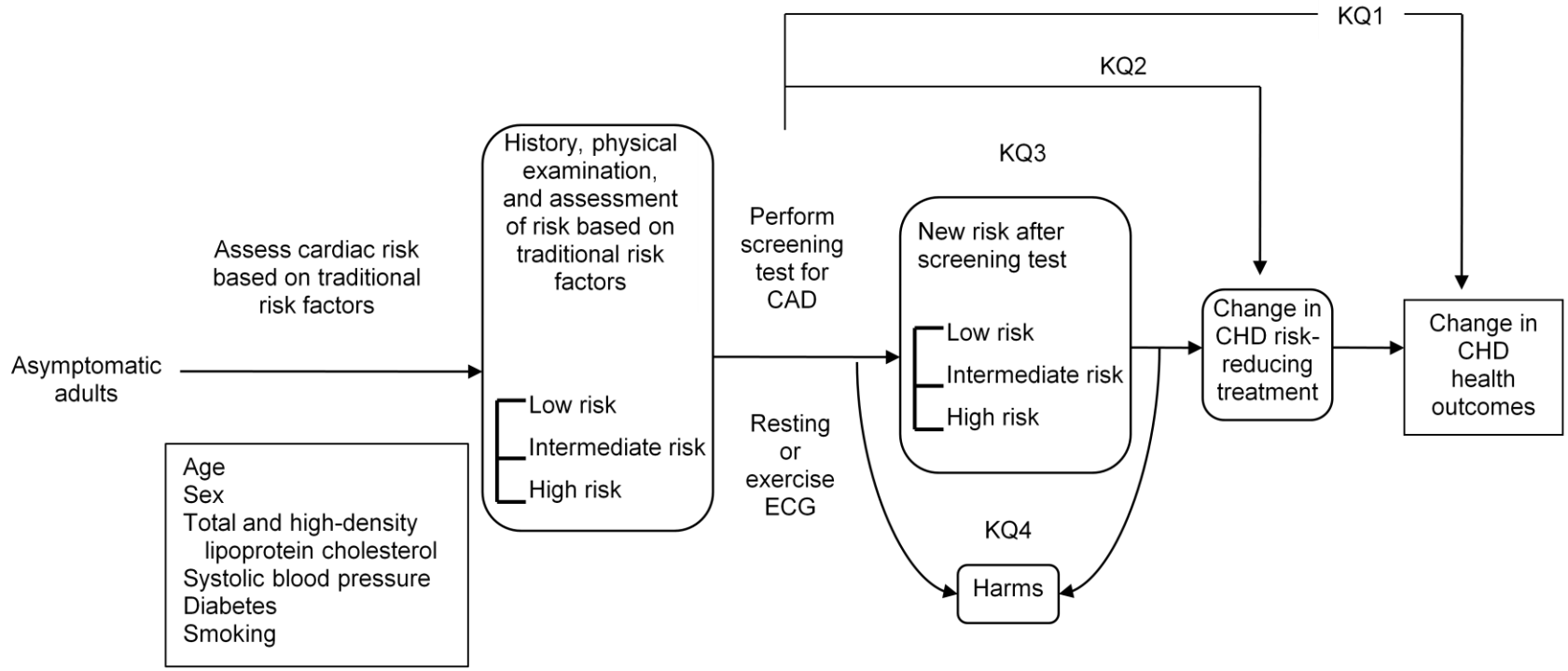
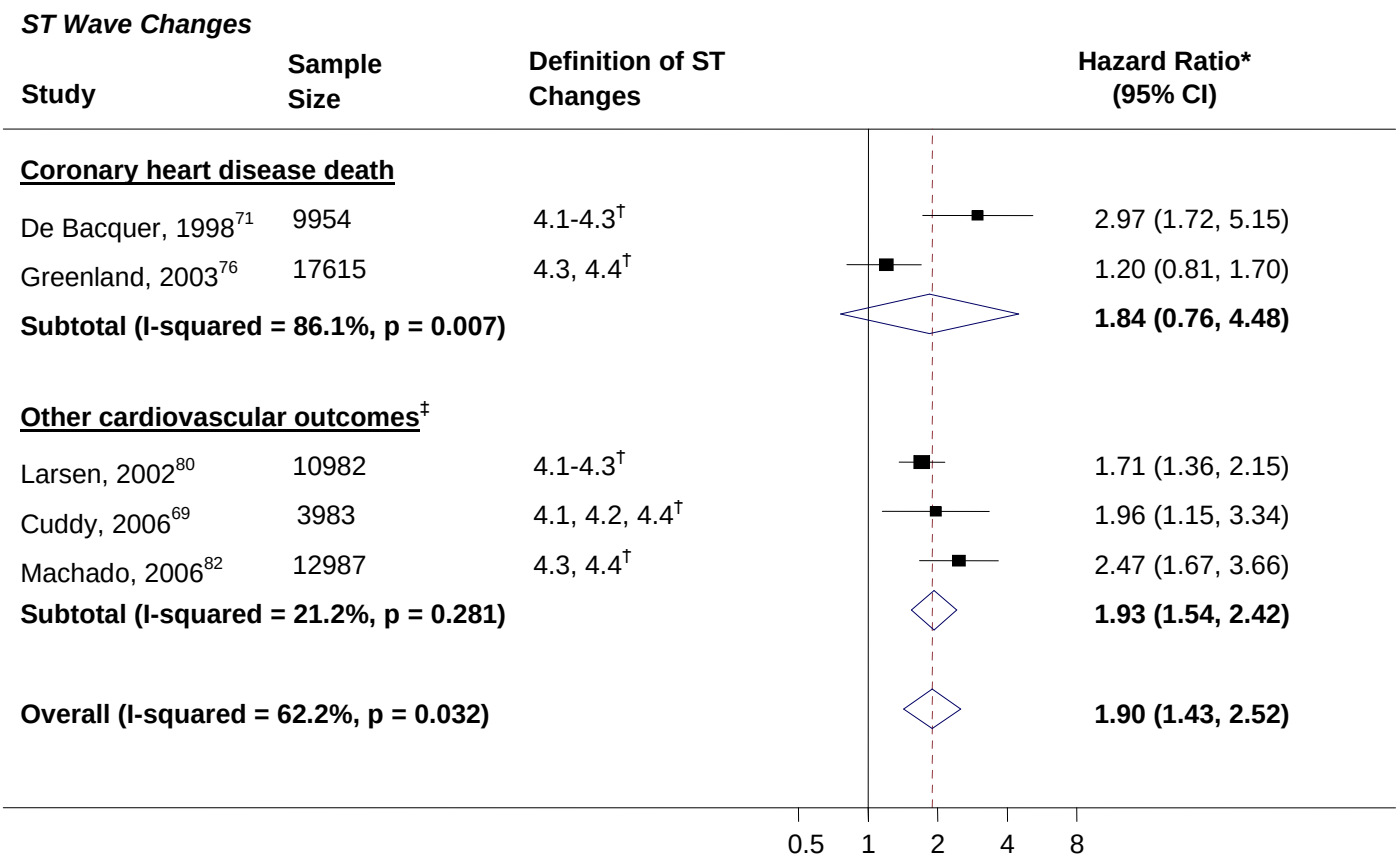
Figure 1. Analytic Framework and Key Questions



Key Questions

1. What are the benefits of screening for abnormalities on resting or exercise electrocardiography compared to no screening on coronary heart disease outcomes?
2. How does the identification of high-risk persons via resting or exercise electrocardiography affect use of treatments to reduce cardiovascular risk?
3. What is the accuracy of resting or exercise electrocardiography for stratifying persons into high-, intermediate-, and low-risk groups?
4. What are the harms of screening with resting or exercise electrocardiography?

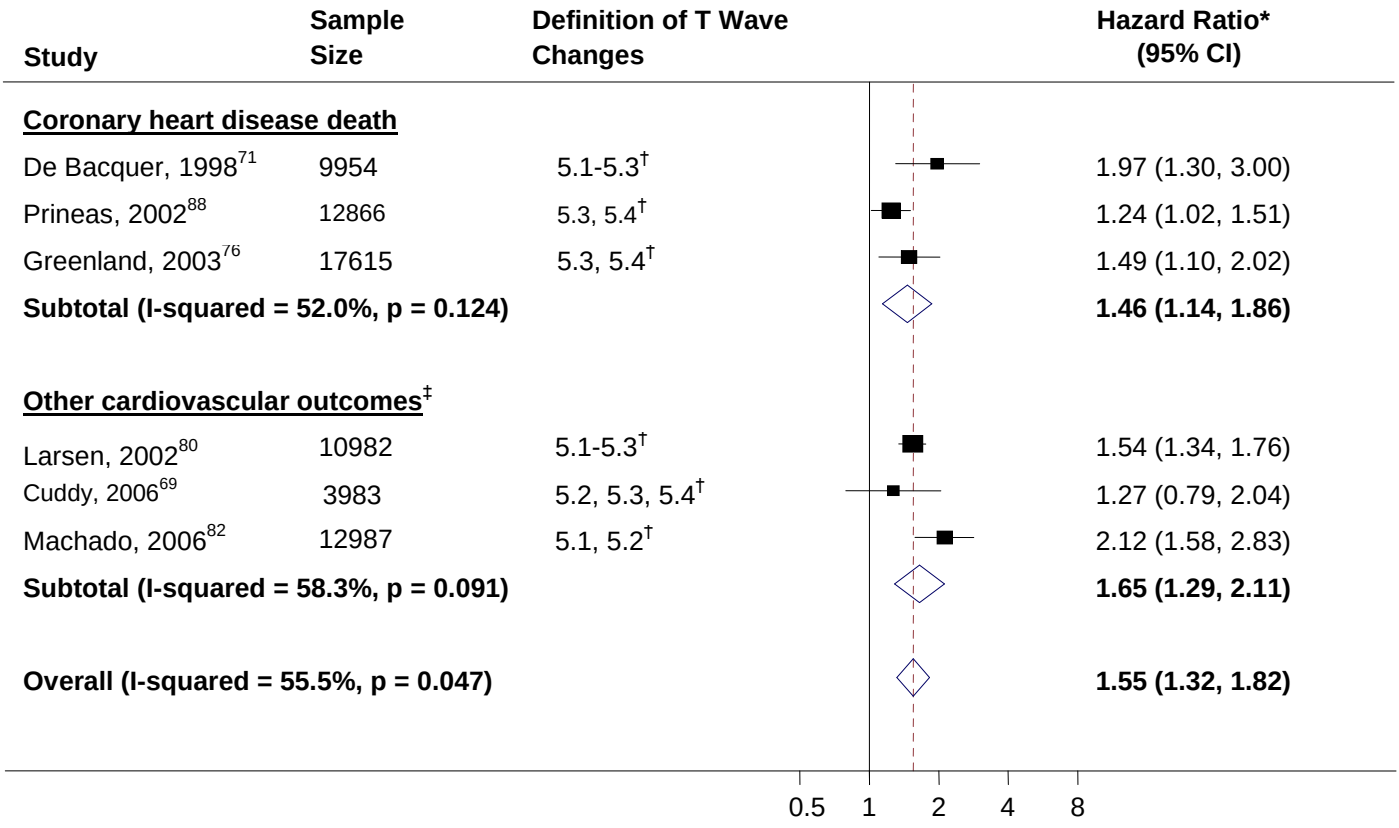
Figure 2. Meta-Analyses of ST and T Wave Changes on Resting ECG as Predictors of Cardiovascular Events



* Adjusted for Framingham risk factors.
† Minnesota codes.
‡ Fatal or nonfatal MI, fatal or nonfatal CHD event (Larsen 2002); sudden, unexpected cardiac death (Cuddy 2006); incident CHD (Machado 2006).

Figure 2. Meta-Analyses of ST and T Wave Changes on Resting ECG as Predictors of Cardiovascular Events

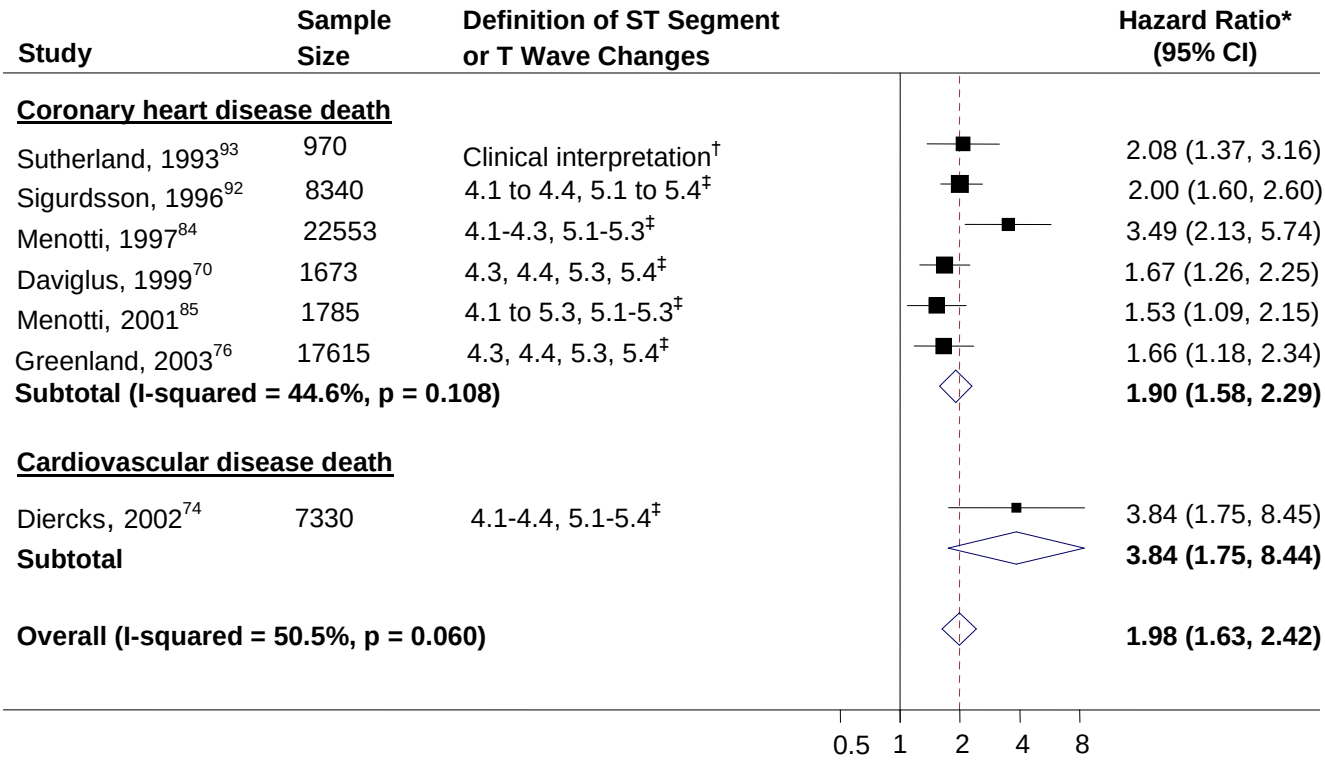
T Wave Changes



* Adjusted for Framingham risk factors.
† Minnesota codes.
‡ Fatal or nonfatal MI, fatal or nonfatal CHD event (Larsen 2002); sudden, unexpected cardiac death (Cuddy 2006); incident CHD (Machado 2006).

Figure 2. Meta-Analyses of ST and T Wave Changes on Resting ECG as Predictors of Cardiovascular Events

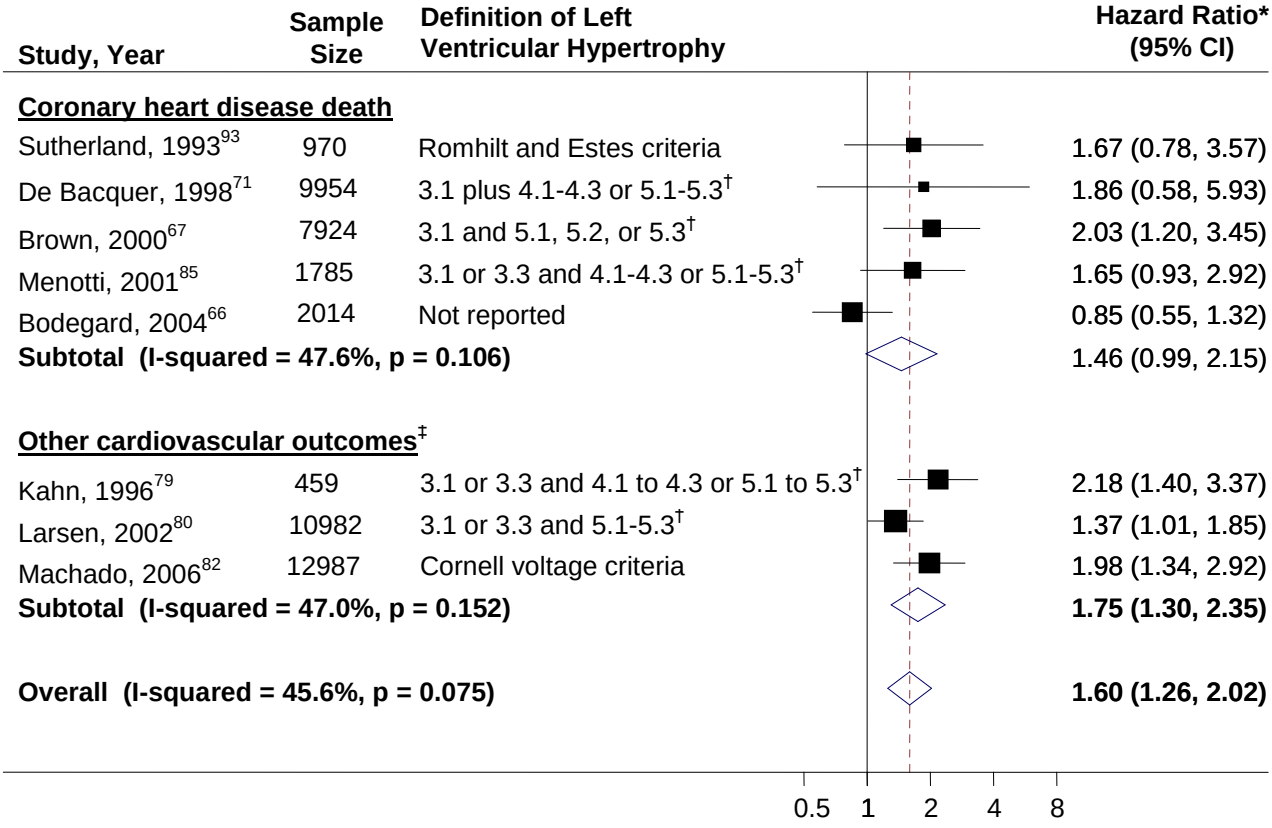
ST or T Wave Changes



* Adjusted for Framingham risk factors.
† 86% concordance with 4.1 to 4.3 and 5.1 to 5.3.
‡ Minnesota codes.

Figure 3. Meta-Analyses of Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

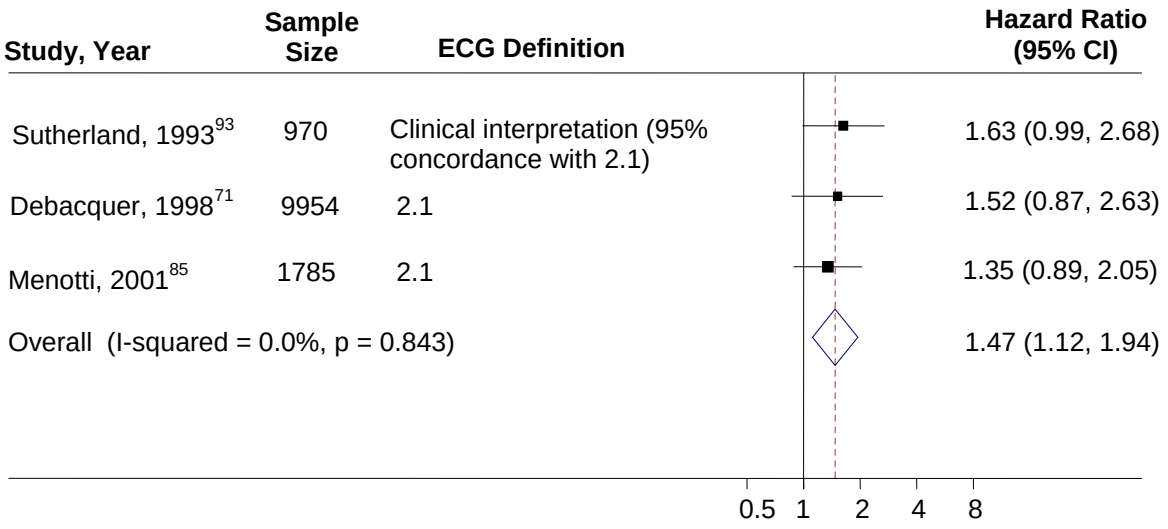
Left Ventricular Hypertrophy Change



* Adjusted for Framingham risk factors.
† Minnesota codes.
‡ MI death, all-cause mortality, cerebrovascular accident mortality, all cardiovascular disease, fatal or nonfatal MI, fatal or nonfatal cerebrovascular accident (Kahn 1996); fatal or nonfatal MI, fatal or nonfatal CHD event (Larsen 2002); incident CHD (Machado 2006).

Figure 3. Meta-Analyses of Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

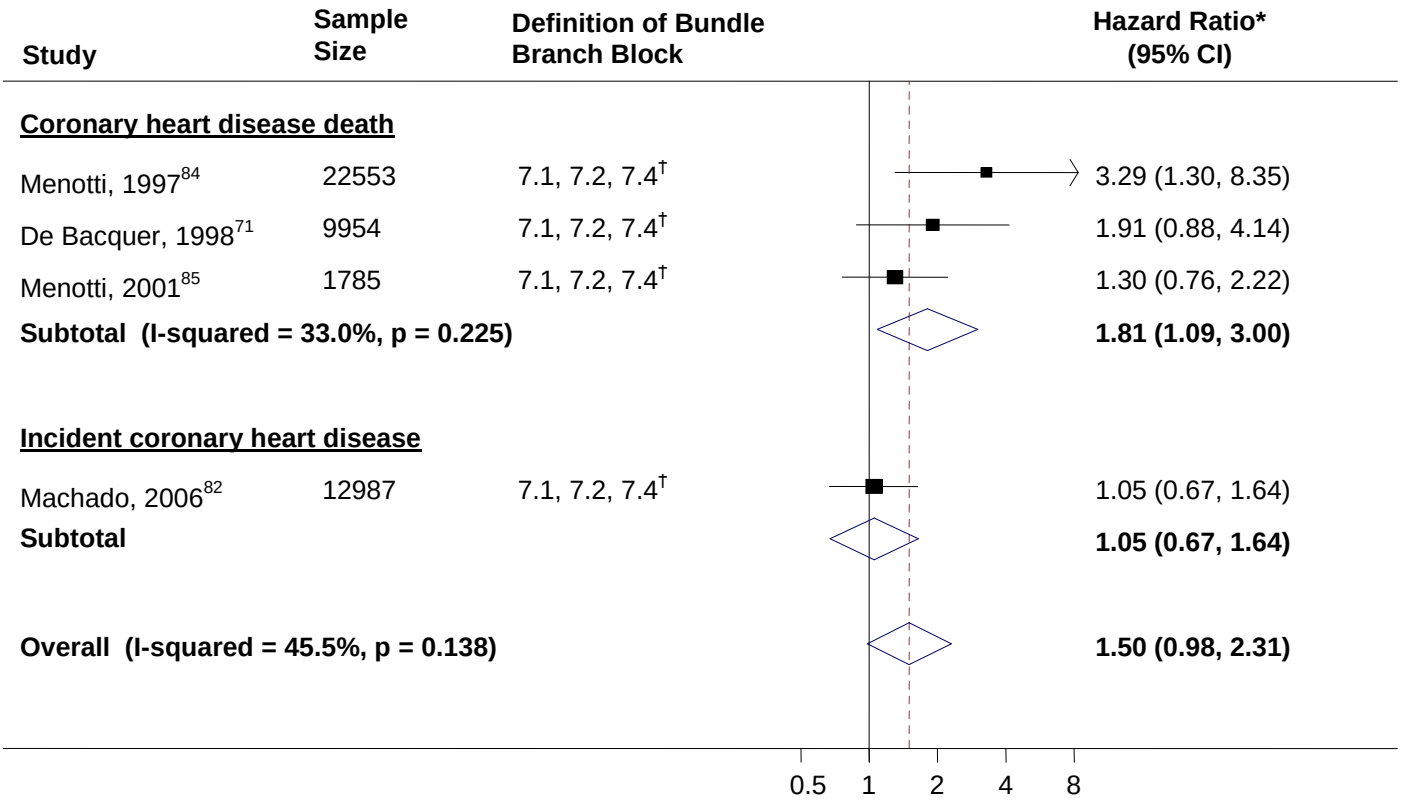
Left Axis Deviation Change



* Adjusted for Framingham risk factors.
† 95% concordance with 2.1.
‡ Minnesota codes.

Figure 3. Meta-Analyses of Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

Bundle Branch Block Change



* Adjusted for Framingham risk factors.
† Minnesota codes.

Figure 4. Meta-Analysis of ST Segment Changes on Exercise ECG as Predictors of Cardiovascular Events

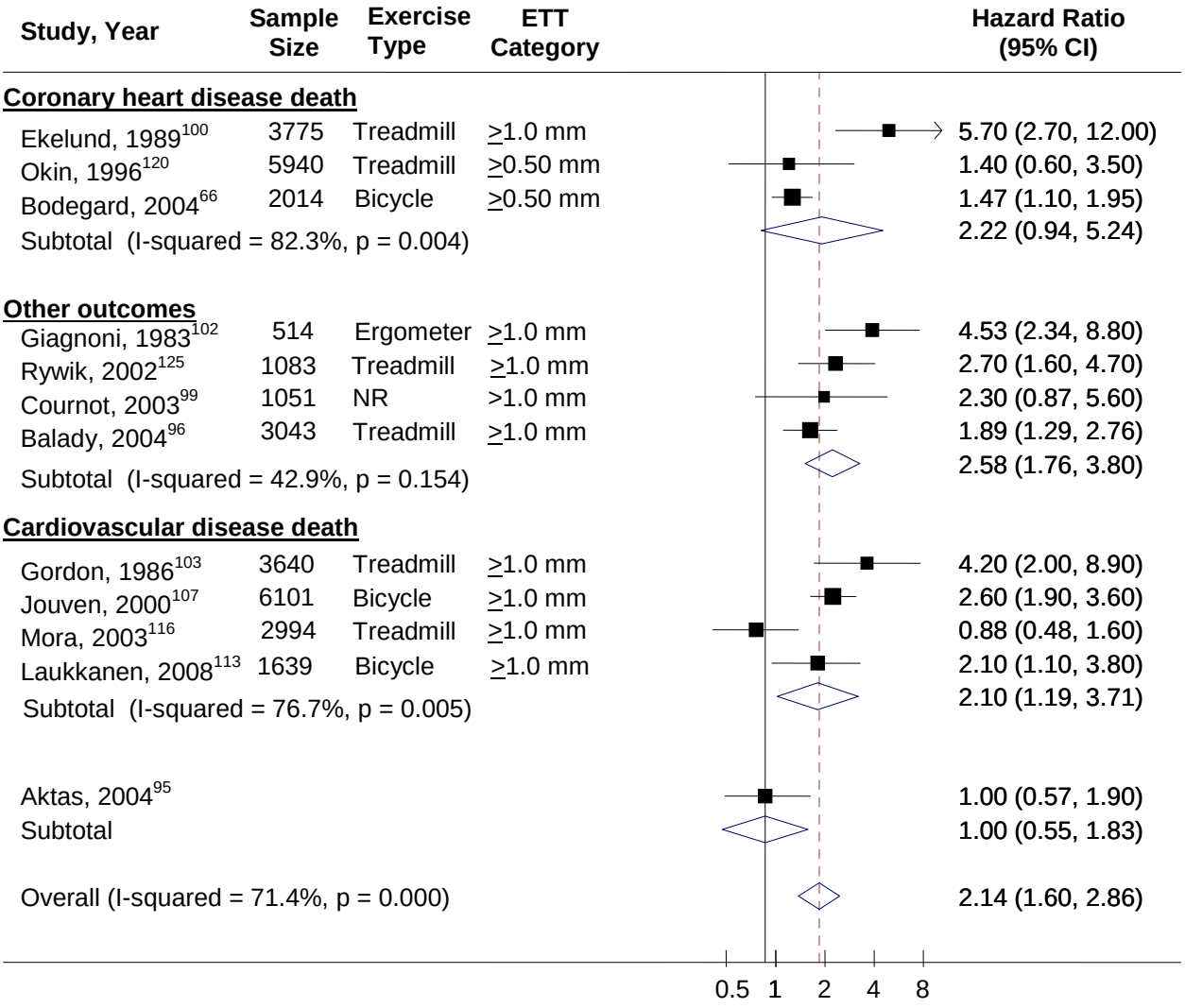
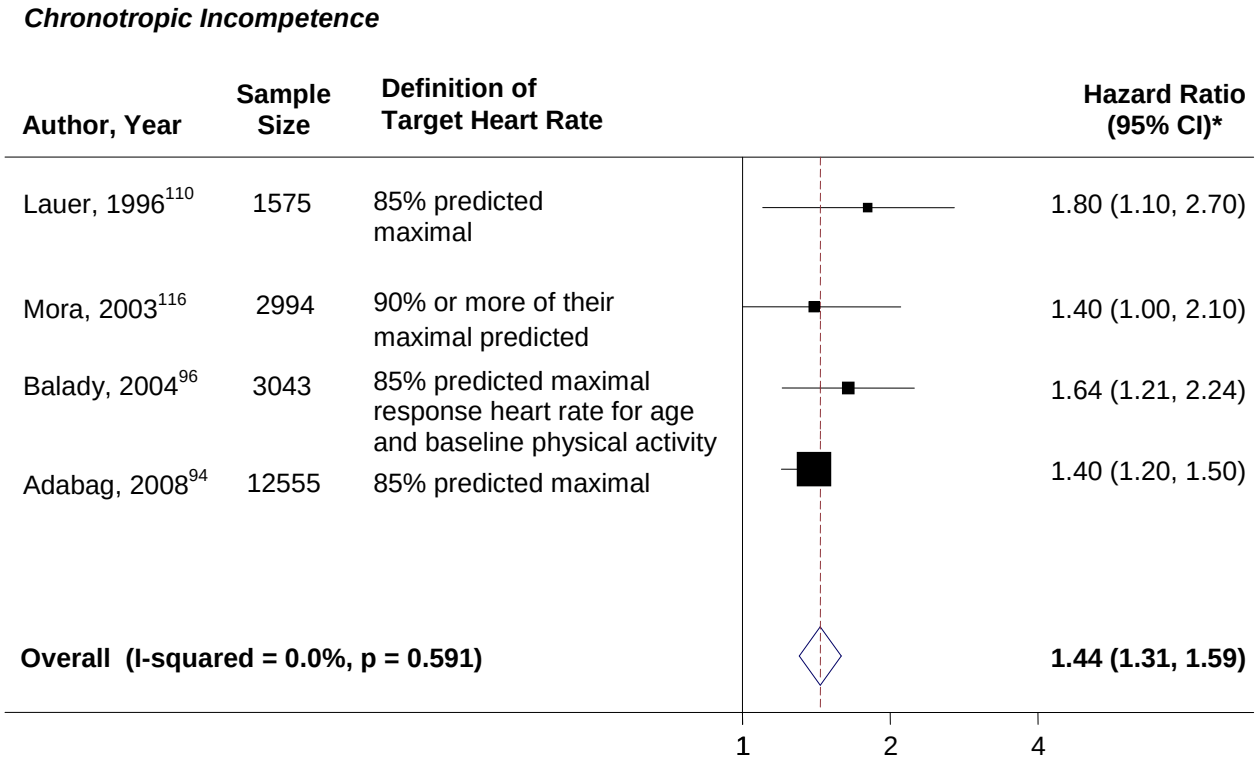


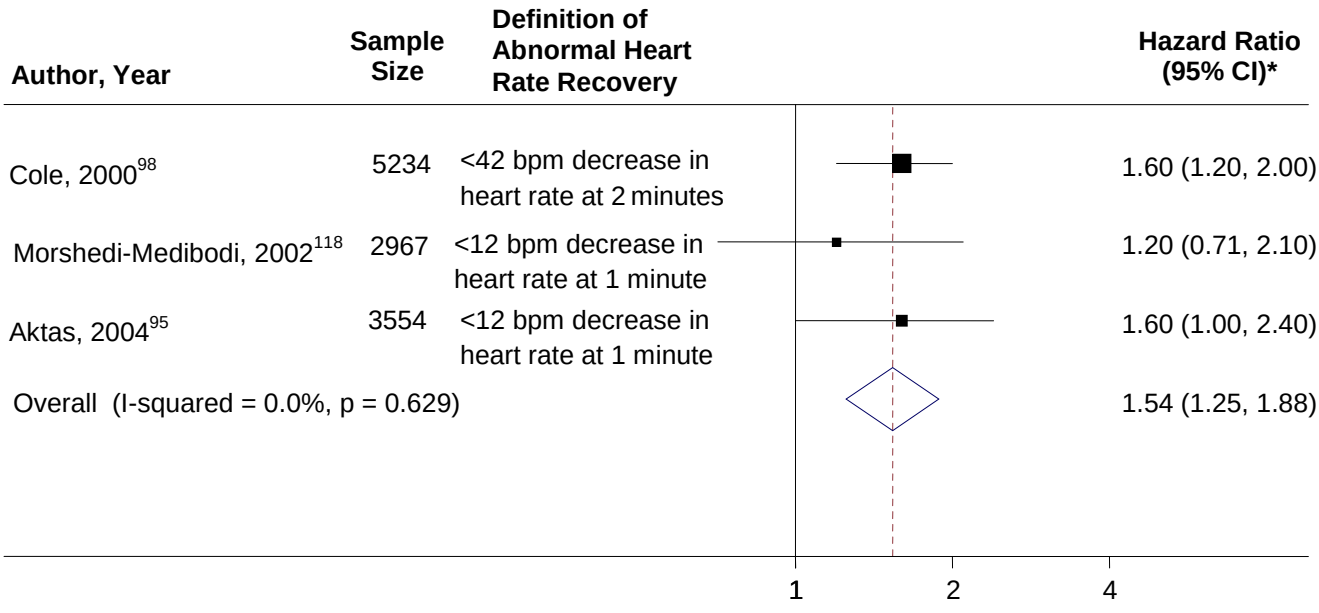
Figure 5. Meta-Analyses of Chronotropic Incompetence and Abnormal Heart Rate Recovery on Exercise ECG as Predictors of Cardiovascular Events



* Adjusted for Framingham risk factors.

Figure 5. Meta-Analyses of Chronotropic Incompetence and Abnormal Heart Rate Recovery on Exercise ECG as Predictors of Cardiovascular Events

Abnormal Heart Rate Recovery



* Adjusted for Framingham risk factors.

Table 1. Summary of Pooled Risk Estimates for Resting or Exercise ECG Abnormalities and Subsequent Cardiovascular Events

Resting ECG abnormality	Number of studies (references)	Pooled adjusted HR (95% CI); Heterogeneity	Exercise ECG abnormality	Number of studies (references)	Pooled adjusted HR (95% CI); Heterogeneity
ST segment abnormalities	5 (69, 71, 76, 80, 82)	1.9 (1.4-2.5); I^2=62%	ST depression with exercise	12 (66, 95, 96, 99, 100, 102, 103, 107, 113, 120, 125, 166)	2.1 (1.6-2.9); I^2=71%
T wave abnormalities	6 (80, 69, 71, 76, 82, 88)	1.6 (1.3-1.8); I^2=56%	Chronotropic incompetence	4 (94, 96, 110, 116)	1.4 (1.3-1.6); I^2=0%
ST or T wave abnormalities	7 (70, 74, 76, 84, 85, 92, 93)	1.9 (1.6-2.4); I^2=50%	Abnormal heart rate recovery*	3 (95, 98, 118)	1.5 (1.3-1.9); I^2=0%
Left ventricular hypertrophy	8 (66, 67, 71, 79, 80, 82, 84, 93)	1.6 (1.3-2.0); I^2=46%	Decreased exercise capacity or fitness	6 (95, 97, 105, 113, 121, 129)	Range, 1.7-3.1 (could not be pooled)
Bundle branch block	4 (71, 82, 84, 85)	1.5 (0.98-2.3); I^2=46%			
Left axis deviation	3 (71, 84, 93)	1.5 (1.1-1.9); I^2=0%			

* Estimate is for all-cause mortality; cardiovascular-specific outcomes could not be pooled.

Abbreviations: CI=confidence interval; ECG=electrocardiography; HR=hazard ratio.

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Bodegard et al, 2004[66]	Study not named Norway Work volunteers	n=2,014 Mean age: 50 yrs (range, 40-59) 100% male Race NR	LVH: 5.3%	22	Age, sex, smoking, SBP, total cholesterol	CHD death: 15% All-cause mortality: 37% Acute MI: 19% Coronary artery bypass graft surgery: 6.0% Stroke: 7.7%	Good
Brown et al, 2000[67]	Second National Health and Nutrition Examination Survey (NHANES II) United States General community	n=7,924 Mean age: 49 yrs (range, 25-74) 48% male 90% white 10% black	LVH: 1.9%	15	Sex, smoking, diabetes, SBP, total cholesterol	CHD death: 3.7% Heart disease death: 5.3%	Fair
Crow et al, 2003[68]	Atherosclerosis Risk in Community (ARIC) Study United States General community	n=14,696 Mean age: 54 yrs (range, 45-64) 43% male 73% white	QTc: continuous variable JTc: continuous variable Wide QRS complex: 3.1%	13	Age, sex, smoking, diabetes, SBP, HDL, LDL	Incident MI or fatal CHD event: 5.6%	Fair
Cuddy et al, 2006[69] Other sources: www.mfus.ca	Manitoba Follow-Up Study Canada Royal Canadian Air Force recruits	n=3,983 Mean age: 31 yrs (range, 20-39) 100% male Race NR	Atrial fibrillation: 7% VPC: 23% Atrioventricular block: 12% Right bundle branch block: 5% Left bundle branch block: 2% LVH: 12% ST and T wave abnormality: 22% (ST), 37% (T wave)	56	Age, sex (100% male), smoking, diabetes, SBP, DBP	Sudden unexpected cardiac death: 4.3%	Fair
Daviglus et al, 1999[70] Other publications: Oglesby, 1963[146]	Chicago Western Electric Study United States Male electric company workers	n=1,673 Mean age: 47 yrs (range, 40-55) 100% male Race NR	Minor ST-T abnormality: 10.3%	29	Age, sex (100% male), smoking, SBP, total cholesterol	CHD death: 21% MI death: 14% CVD death: 28% All-cause mortality: 53%	Fair
De Bacquer et al, 1998[71]	Belgian Inter-University Research on Nutrition and Health (BIRNH) Study Belgium General community	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Race NR	Any ECG abnormality: 29% Major ECG abnormality: 29% Minor ECG abnormality: 3.6% Ischemic ECG abnormality: 10% ST depression: 2% Abnormal T wave: 8% Arrhythmia: 6% Bundle branch block: 1% LVH: 0.6% Left axis deviation: 4%	10	Age, sex, smoking, diabetes, SBP, HDL, LDL, total cholesterol	CHD death: 1.3% CVD death: 2.4% All-cause mortality: 7.9%	Good

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Denes et al, 2007[72]	Women's Health Initiative United States Clinical trial enrollees	n=14,749 Mean age: 63 yrs (range, 50-79) 0% male 84% white	Major ECG abnormality: 6.2% Minor ECG abnormality: 28%	5.2	Age, sex (100% female), smoking, diabetes, hypertension, statin use	CHD events: 4.0% CVD events: 1.7%	Good
Dhingra et al, 2006[73]	Framingham Heart Study United States General community	n=1,759 Mean age: 70 yrs (SD, 7) 37% male Race NR	QRS duration 100-119 ms (incomplete bundle branch block): 17% QRS duration ≥120 ms (complete bundle branch block): 6%	12.7	Age, sex, smoking, diabetes, hypertension, HDL, total cholesterol	CHF: 18% (men, 18%; women, 19%)	Good
Diercks et al, 2002[74]	Prevention of Renal and Vascular End-Stage Disease Study The Netherlands General community	n=7,330 Mean age: 48 yrs (range, 28-75) 50% male Race NR	ST-T changes: 17%	3	Age, sex, smoking, diabetes, hypertension, total cholesterol	CVD death: 0.3% All-cause mortality: 1.2%	Fair
Gottdiener et al, 2000[75] Other publications: Furberg et al, 1992[147]	Cardiovascular Health Study United States General community	n=4,652 (analyzed group with no prevalent CHD) Mean age: 73 yrs (range, 65-100; entire cohort, including prevalent CHD) 40% male 85% nonblack	Major Q/QS wave: 5.2% LVH: 4.2% Isolated major ST-T wave abnormality: 6.3% Atrial fibrillation: 3.2% Atrioventricular block: 5.3% Ventricular conduction defect: 8.7% (based on entire study cohort)	6.3	Age, sex, smoking, diabetes, hypertension, HDL, LDL, total cholesterol	CHF: 8.5%	Good
Greenland et al, 2003[76]	Chicago Heart Association Detection Project in Industry United States Work-based	n=17,615 Mean age: 50 yrs (range, 40-64) 55% male 95% white	Any ST changes: 3.6% men; 5.4% women Minor T wave abnormality: 1.6% men; 1.9% women Minor ST depression: 1.2% men; 1.5% women	22	Age, sex, smoking, blood glucose, SBP, total cholesterol	CHD death: 7.1% CVD death: 9.9%	Fair
Jouven et al, 2005[78]	Paris Protective Study I France Civil servants	n=5,713 Mean age: 48 yrs (range, 42-53) 100% male Race NR	High (>75 bpm) resting heart rate: 8%	23	Age, sex (100% male), smoking, diabetes, SBP, cholesterol	Fatal MI (sudden death): 1.4% Fatal MI (nonsudden death): 2.3% All-cause mortality: 27%	Good

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Kahn et al, 1996[79]	Bronx Longitudinal Aging Study United States General community	n=459 Mean age: 79 yrs (range, 75-85) 35% male >95% white	LVH: 9.2%	10	Age, sex, smoking, hypertension, total cholesterol	CVD death: 19% MI death: 16% All-cause mortality: 34% Cerebrovascular accident mortality: 3.3% All cardiovascular disease: 56% Fatal or nonfatal MI: 14% Fatal or nonfatal cerebrovascular accident: 7.6%	Fair
Larsen et al, 2002[80]	Copenhagen City Heart Study Denmark General community	n=10,982 Mean age: 54 yrs (range, 35-74) 45% male >98% white	LVH: 11% T wave inversion: 3.4% ST-T depression and T wave inversion: 0.7% LVH + T wave inversion: 0.8% LVH + ST-T depression + T wave inversion: 0.7%	21	Age, sex, smoking, diabetes, SBP, total cholesterol	CVD death: 18% Fatal or nonfatal MI: 10% Fatal or nonfatal CHD events: 19%	Good
Liao et al, 1988[81]	Chicago Heart Association Detection Project in Industry United States Work-based	n=17,633 Mean age: 51 yrs 55% male 100% white	Major abnormality: 11.1% Minor abnormality: 6% Any abnormality: 17.5%	11.5	Age, sex, smoking, diabetes, DBP, total cholesterol	CHD death: 2.9% Cardiovascular death: 3.8% All-cause mortality: 7.8%	Fair

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Macfarlane et al, 2007[77]	West of Scotland Coronary Prevention Study (WOSCOPS) United Kingdom	n=6,595 Mean age: 55 yrs 100% male Race NR	Left axis deviation MN code 2.1: 2.7% Right axis deviation MN code 2.2 or 2.3: 0.5% High voltage left ventricular lead MN code 3.1: 5.1% High voltage right ventricular lead MN code 3.2: 0.06% ST abnormality MN code 4.2 or 4.3: 2.3% T wave abnormality MN code 5.2 or 5.3: 7.9% Right bundle branch block MN code 7.2.1 or 7.8: 1% Definite or probable LVH MN code 3.1 + ST or T wave abnormalities: 0.6%; 0.3% Possible LVH MN code 3.1 or 3.3: 7.3% Minor ECG abnormality MN code 4.2, 4.3, 5.2, or 5.3: 8.2% T wave inversion T wave amplitude <0 mV: 2.6%	4.9 yrs	Age, sex (100% male), smoking, diabetes, hypertension, HDL, total cholesterol	Definite MI: 5.4% Suspected MI:1.5% All-cause mortality: NR	Fair
Machado et al, 2006[82] Other publications: ARIC investigators 1989[148]	Atherosclerosis Risk in Communities (ARIC) Study United States General community	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male 74% white	Minor Q wave: 2% Prolonged QTc interval: 9% LVH (Cornell): 2% LVH (ST-T strain pattern): 2% Major ventricular conduction defect: 2% Major ST depression: <1% Minor ST depression: 1% ST elevation: 1% Major T wave findings: 4% Any ECG abnormality: 18.1%	11.6	Age, sex, smoking, diabetes, SBP, DBP, HDL, LDL	Incident CHD: 5.6%	Fair
Massing et al, 2006[83]	Atherosclerosis Risk in Communities (ARIC) Study United States General community	n=15,070 Mean age: 54 yrs (range, 45-64) 45% male 74% white	Ventricular premature contractions: 6.2%	>10 (11.6 in other ARIC publi-cations)	Age, sex, smoking, diabetes, hypertension, HDL, LDL	Asymptomatic population CHD death: 1.6% CHD events: 9.6% All-cause mortality: 10.5%	Fair

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Menotti et al, 1997[85] Other publications: RIFLE Research Group, 1993[149]	Risk Factors and Life Expectancy (RIFLE) Study Italy General community	n=22,553 Mean age NR (50% 50-69 yrs) 54% male Race NR	Q-QS wave: 0.8% ST-T changes: 5.7% High R wave: 4.7% Arrhythmia: 1.2% Bundle branch block: 1.2%	6	Age, sex, smoking, SBP, total cholesterol	<u>All-cause mortality (by subgroup)</u> Q-QS: 1.6% ST-T: 1.6% High R wave: 0.9% Arrythmia: 1.5% Block: 1.3%	Fair
Menotti et al, 2001[84] Other publications: Menotti et al, 1996[156]	FINE Study Finland, the Netherlands, and Italy General community	n=1,785 Mean age NR (range, 65-84 yrs) 100% male Race NR	Q-QS wave: 6.8% ST-T abnormality: 22% High R wave: 15% Left axis deviation: 13% Arrhythmia: 8.5% Bundle branch block: 7.3% Major abnormality: 8.3% Minor abnormality: 39%	10	Age, sex (100% male), smoking hypertension, total cholesterol	CHD death: 9%	Fair
Moller et al, 2007[86]	Uppsala Longitudinal Study of Adult Men Sweden General community	n=2,322 Age: 50 yrs (all were age 50 at enrollment) 100% male Race NR	Q/QS wave pattern: 1.3% LVH: 1.2% ST segment depression: 2.3% T wave abnormality: 5.9% Atrial fibrillation: 0.3%	NR; followup >20 yrs, max 32	Age, sex (100% male), smoking, diabetes, hypertension, HDL, LDL	Fatal and nonfatal stroke: 15% Fatal and nonfatal ischemic stroke: 10%	Fair
Prineas et al, 2001[87]	Multiple Risk Factor Intervention Trial (MRFIT) United States Clinical trial enrollees	n=12,866 Mean age: 46 yrs (range, 35-57), based on entire cohort 100% male 93% white	New (incident) LVH on 6-yr followup ECG based on various criteria: Sokolow-Lyon: 6% Cornell voltage: 1% Cornell product: 2% Novacode: 5% MN code 3.1 or 3.3 + 5.1, 5.2, or 5.3: 4% Significant increase in LVH on 6-yr followup ECG based on various criteria: Sokolow-Lyon: 0.5% Cornell voltage: 3.5% Cornell product: 2.8% Novacode: 1.4% Σ12 product (sum of peak-to-peak amplitudes of QRS complexes except lead avR, x QRS duration): 0.8%	16	Age, sex (100% male), DBP, total cholesterol, smoking	CHD death: 4.8% CVD death: 6.6%	Good

Table 2. Cohort Studies of Resting ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Country Population	Sample size Demographics	ECG abnormalities evaluated; Prevalence	Mean followup (yrs)	Framingham risk factors adjusted	All-cause mortality and incident cardiovascular events	Quality
Prineas et al, 2002[88]	Multiple Risk Factor Intervention Trial (MRFIT) United States Clinical trial enrollees	n=12,866 Mean age: 46 yrs (range, 35-57), based on entire cohort 100% male 93% white	Minor T wave abnormality: 7.1%	18	Age, sex (100% male), smoking, diabetes, DBP, HDL, LDL	CHD death: 7.3% CVD death: 10% All-cause mortality: 23%	Good
Rautaharju et al, 2006a and 2006b[89,90]	Women's Health Initiative (WHI) United States Clinical trial enrollees	n=35,715 Mean age: 62 yrs (range, 50-79) 0% male 82% white	QRS/T angle STV5 TV1 TV5 QTrr STV5 gradient MI by ECG Cornell voltage QRS nondipolar voltage Ultrashort heart rate variability	6.2	Age, sex (100% female), smoking, diabetes, SBP	CHD death: 0.3% Incident CHF: 1.0% All-cause mortality: 2.4% Nonfatal and fatal CHD events: 1.4%	Fair
Rautaharju et al, 2006c[91]	Cardiovascular Health Study United States General community	n=4,085 Mean age: 73 yrs (inclusion criteria age ≥65) 37% male 85% nonblack	ST depression: continuous variable ECG-left ventricular mass: continuous variable QRS/T angle: continuous variable	9.1	Age, sex, smoking, diabetes, SBP (hypertensive status or use of anti-hypertensives)	CHD death: 7.2% All-cause mortality: 35%	Fair
Sigurdsson et al, 1996[92]	Reykjavik Study Iceland General community	n=8,340 Mean age: 52 yrs (range, 35-60) 100% male Race NR	ST-T changes: 5%	4 to 24	Age, sex (100% male), smoking, fasting blood glucose, hypertension (SBP and DBP), total cholesterol	Silent ST-T segment group Angina: 9% MI: 5% All-cause mortality: 12%	Fair
Sutherland et al, 1993[93]	Charleston Heart Study United States General community	n=993 Mean age: 48 yrs (range, 35-74) 100% male 66% white	Major ECG abnormality: 9% Minor ECG abnormality: 14% Left axis deviation: 8% Early repolarization: 23% Nonspecific ST-T changes: 16% LVH: 4%	30	Age, sex (100% male), smoking, diabetes, SBP, total cholesterol	CHD death: 19%	Good

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CHF=congestive heart failure; CVD=cardiovascular disease; DBP=diastolic blood pressure; ECG=electrocardiography; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LVH=left ventricular hypertrophy; MN=Minnesota; MI=myocardial infarction; NR=not reported; SD=standard deviation; SBP=systolic blood pressure; VPC=ventricular premature complex; yrs=years.

Table 3. ST and T Wave Changes on Resting ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of segment abnormality; Prevalence	Risk associated with segment abnormality compared to no abnormality (95% CI)
ST Wave Change			
Cuddy et al, 2006[69] *Manitoba Follow-Up Study*	n=3,983 Mean age: 31 yrs (range, 20-39) 100% male Mean followup: 56 yrs	MN codes 4.1, 4.2, 4.4: 22%	Sudden unexpected cardiac death First 5 yrs following detection of ST changes: HR, 2.5 (1.5-4.4) >5 yrs since detection of ST changes: HR, 2.0 (1.2-3.3)*
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN codes 4.1, 4.2, 4.3: 2%	CHD death: HR, 3.0 (1.7-5.2)*
Greenland et al, 2003[76] *Chicago Heart Association Detection Project in Industry*	n=17,615 Mean age: 50 yrs (range, 40-64) 55% male Mean followup: 22 yrs	MN codes 4.3, 4.4: 1.2% men; 1.5% women	CHD death: HR, 1.2 (0.81-1.7)* CVD death: HR, 1.1 (0.81-1.5) All-cause mortality: HR, 1.0 (0.84-1.3)
Larsen et al, 2002[80] *Copenhagen City Heart Study*	n=10,982 Mean age: 54 yrs (range, 35-74) 45% male Mean followup: 21 yrs	MN codes 4.1, 4.2, 4.3: 0.7%	CVD death: HR, 1.7 (1.4-2.2)* MI (fatal and nonfatal): HR, 1.7 (1.2-2.3)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities Study (ARIC)* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 11.6 yrs	MN codes 4.3, 4.4: 1%	Nonfatal MI or CHD death: HR, 2.5 (1.7-3.7)*
Moller et al, 2007[86] *Uppsala Longitudinal Study of Adult Men*	n=2,322 Mean age: 50 yrs (all 50 yrs) 100% male Mean followup: NR (followup >20 yrs with max 32 yrs)	MN codes 4.1, 4.2: 2.3%	Fatal and nonfatal stroke: HR, 3.4 (2.1-5.4); 0-30 yrs followup Fatal and nonfatal ischemic stroke: HR, 4.4 (2.6-7.4); 0-30 yrs followup
T Wave Change			
Cuddy et al, 2006[69] *Manitoba Follow-Up Study*	n=3,983 Mean age: 31 yrs (range, 20-39) 100% male Mean followup: 56 yrs	MN codes 5.2, 5.3, 5.4: 37%	Sudden unexpected cardiac death First 5 yrs following detection of T wave changes: HR, 2.1 (1.2-3.5) >5 yrs since detection of T wave changes: HR, 1.3 (0.79-2.0)*
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN codes 5.1, 5.2, 5.3: 8%	CHD death: HR, 2.0 (1.3-3.0)*
Greenland et al, 2003[76] *Chicago Heart Association Detection Project in Industry*	n=17,615 Mean age: 50 yrs (range, 40-64) 55% male Mean followup: 22 yrs	MN codes 5.3, 5.4: 1.6% men; 1.9% women	CHD death: HR, 1.5 (1.1-2.0)* CVD death: HR, 1.5 (1.1-1.9) All-cause mortality: HR, 1.1 (0.93-1.4)

Table 3. ST and T Wave Changes on Resting ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of segment abnormality; Prevalence	Risk associated with segment abnormality compared to no abnormality (95% CI)
Larsen et al, 2002[80] *Copenhagen City Heart Study*	n=10,982 Mean age: 54 yrs (range, 35-74) 45% male Mean followup: 21 yrs	MN codes 5.1, 5.2, 5.3: 3.4%	CVD death: HR, 1.5 (1.3-1.8)* MI (fatal and nonfatal): HR, 1.3 (1.1-1.6)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities Study (ARIC)* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 11.6 yrs	MN codes 5.1, 5.2: 4%	Nonfatal MI or CHD death: HR 2.1 (1.6 to 2.8)*
Moller et al, 2007[86] *Uppsala Longitudinal Study of Adult Men*	n=2,322 Age: 50 yrs (all 50 yrs) 100% male Mean followup: NR (followup >20 yrs with max 32 yrs)	MN codes 5.1, 5.2, 5.3: 5.9%	Fatal and nonfatal stroke: NS; 0-30 yrs followup (data NR) Fatal and nonfatal ischemic stroke: NS; 0-30 yrs followup (data NR)
Prineas et al, 2002[88] *Multiple Risk Factor Intervention Trial (MRFIT)*	n=12,866 Mean age: 46 yrs (range, 35-57), based on entire cohort 100% male Mean followup: 18 yrs	MN codes 5.3, 5.4: 7.1%	CHD death: HR, 1.2 (1.0-1.5)* CVD death: HR, 1.3 (1.1-1.5) All-cause mortality: HR, 1.1 (1.0-1.2)
ST or T Wave Change			
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti et al, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	MN codes 4.1, 4.2, 4.3, 5.1, 5.2, 5.3: 26%	CHD death: HR, 1.5 (1.1-2.2)*
Sigurdsson et al, 1996[92] *Reykjavik Study*	n=8,340 Mean age: 52 yrs (range, 35-60) 100% male Followup: 4-24 yrs	MN codes 4.1 to 4.4; 5.1 to 5.4: 5%	CHD death: HR, 2.0 (1.6-2.6)* Angina or MI: HR, 1.6 (1.0-2.8)
Sutherland et al, 1993[93] *Charleston Heart Study*	n=993 Mean age: 48 yrs (range, 35-74) 100% male Mean followup: 30 yrs	Clinical interpretation (86% concordance with MN codes 4.1 to 4.3 and 5.1 to 5.3): 16%	<u>White men, black men</u> CHD death*: HR, 2.2 (1.2-3.8); HR, 2.0 (1.1-3.7) All-cause mortality: HR, 1.8 (1.2-2.6); HR, 1.1 (0.81-1.6)

*Outcome included in meta-analysis.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; MI=myocardial infarction; MN=Minnesota; NR=not reported; NS=not significant; yrs=years.

Table 4. Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition Prevalence	Risk associated with LVH, left axis deviation, and bundle branch block compared to none (95% CI)
Left Ventricular Hypertrophy			
Bodegard et al, 2004[66] *Study not named*	n=2,014 Mean age: 50 yrs (range, 40-59) 100% male Mean followup: 22 yrs	Criteria not described: 5.3%	CHD death: HR, 0.85 (0.55 to 1.3)*
Brown et al, 2000[67] *Second National Health and Nutrition Examination Survey (NHANES II)*	n=7,924 Mean age: 49 yrs (range, 25-74) 48% male Mean followup: 15 yrs	MN codes 3.1 or 3.3 and 4.1 to 4.3 or 5.1 to 5.3	CHD death: HR, 2.0 (1.2 to 3.4)*
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN codes 3.1 plus 4.1 to 4.3 or 5.1 to 5.3: 0.6%	CHD death: HR, 1.9 (0.58 to 5.9)*
Kahn et al, 1996[79] *Bronx Longitudinal Aging Study*	n=459 Mean age: 79 yrs (range, 75-85) 35% male Mean followup: 10 yrs	MN codes 3.1; 3.3 + 4.1 to 4.3 or 5.1 to 5.3: 9.2%	CVD death: HR, 2.2 (1.4 to 3.4)* All-cause mortality: HR, 0.81 (0.54 to 1.2) MI death: HR, 2.7 (1.4 to 5.3) CVA death: HR, 2.5 (0.73 to 8.4) MI (fatal or nonfatal): HR, 2.3 (1.4 to 4.0) CVA (fatal or nonfatal): HR, 1.6 (0.68 to 4.0)
Larsen et al, 2002[80] *Copenhagen City Heart Study*	n=10,982 Mean age: 54 yrs (range, 35-74) 45% male Mean followup: 21 yrs	MN codes 3.1 or 3.3 and 5.1 to 5.3: 0.8%	CVD death: HR, 1.4 (1.0 to 1.8)* MI (fatal and nonfatal): HR, 1.6 (1.0 to 2.3)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities (ARIC) Study* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 11.6 yrs	Cornell (men >28 mm; women >22 mm): 2% ST-T strain pattern (MN codes 3.1 or 3.3 + 4.3 or 4.2 or 4.1.1 or 4.1.2 or 5.1 to 5.3): 2%	<u>Nonfatal MI or CHD death</u> Cornell criteria: HR, 2.0 (1.3 to 2.9)* ST-T strain pattern criteria: HR, 2.3 (1.2 to 4.3) for black women; HR, 1.1 (0.50 to 2.4) for black men; HR, 2.8 (0.69 to 12) for white women; HR, 6.5 (3.3 to 13) for white men
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti et al, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	MN codes 3.1 or 3.3, plus 4.1 to 4.3 or 5.1 to 5.3: 6.3%	CHD death: HR, 1.6 (0.93 to 2.9)*
Moller et al, 2007[86] *Uppsala Longitudinal Study of Adult Men*	n=2,322 Age: 50 yrs (all 50 yrs) 100% male Mean followup: NR (followup >20 yrs with max 32 yrs)	MN codes 3.1, 3.3 + 4.1, 4.2: 1.2%	Fatal and nonfatal stroke: NS (data NR) Fatal and nonfatal ischemic stroke: NS (data NR)

Table 4. Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition Prevalence	Risk associated with LVH, left axis deviation, and bundle branch block compared to none (95% CI)
Prineas et al, 2001[87] *Multiple Risk Factor Intervention Trial (MRFIT)*	n=12,866 Mean age: 46 yrs (range, 35-57), based on entire cohort 100% male Mean followup: 10 yrs (from 6-yr followup ECG)	New (incident) LVH on 6-yr followup ECG, Sokolow-Lyon: 6% Cornell voltage: 1% Cornell product: 2% Novacode: 5% MN codes 3.1 or 3.3 + 5.1 to 5.3: 4% Significant increase in LVH on 6-yr followup ECG, Sokolow-Lyon: 0.5% Cornell voltage: 3.5% Cornell product: 2.8% Novacode: 1.4% Σ12 product (sum of peak-to-peak amplitudes of QRS complexes x QRS duration): 0.8%	**New (incident) LVH:** CHD death Sokolow-Lyon: HR, 1.5 (1.1 to 2.1) Cornell voltage: HR, 3.9 (2.5 to 6.0) Cornell product: HR, 2.9 (2.0 to 4.1) Novacode: HR, 3.8 (3.0 to 4.8) MN codes 3.1 or 3.3 + 5.1 to 5.3: HR, 2.6 (1.4 to 3.5) CVD death Sokolow-Lyon: HR, 1.6 (1.2 to 2.1) Cornell voltage: HR, 4.4 (3.1 to 6.3) Cornell product: HR, 3.0 (2.2 to 4.0) Novacode: HR, 3.5 (2.8 to 4.2) MN codes 3.1 or 3.3 + 5.1 to 5.3: HR, 2.5 (2.0 to 3.3) **Significant increase in LVH:** CHD death Sokolow-Lyon: HR, 1.3 (0.5 to 3.6) Cornell voltage: HR, 2.2 (1.6 to 3.0) Cornell product: HR, 3.1 (2.3 to 4.2) Novacode: HR, 4.5 (3.2 to 6.5) Σ12 product: HR, 2.4 (1.6 to 4.2) CVD death Sokolow-Lyon: HR, 1.2 (0.5 to 2.9) Cornell voltage: HR, 1.3 (1.0 to 1.6) Cornell product: HR, 3.4 (2.6 to 4.3) Novacode: HR, 4.8 (3.6 to 6.4) Σ12 product: HR, 2.3 (1.4 to 3.8)
Sutherland et al, 1993[93] *Charleston Heart Study*	n=993 Mean age: 48 yrs (range, 35-74) 100% male Mean followup: 30 yrs	Romhilt and Estes criteria (point system): 4%	White men, black men CHD death*: HR, 5.6 (1.2 to 25); HR, 1.1 (0.46 to 2.7) All-cause mortality: HR, 5.5 (2.0 to 15); HR, 0.97 (0.60 to 1.6)
Left Axis Deviation			
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN code 2.1: 4.2%	CHD death: HR, 1.5 (0.87 to 2.6)*
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti et al, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	MN code 2.1: 12%	CHD death: HR, 1.4 (0.89 to 2.0)*

Table 4. Left Ventricular Hypertrophy, Left Axis Deviation, and Bundle Branch Block on Resting ECG as Predictors of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition Prevalence	Risk associated with LVH, left axis deviation, and bundle branch block compared to none (95% CI)
Sutherland et al, 1993[93] *Charleston Heart Study*	n=993 Mean age: 48 yrs (range, 35-74) 100% male Mean followup: 30 yrs	Clinical interpretation, not specified (95% concordance with MN code 2.1): 8%	White men, black men CHD death*: HR, 1.5 (0.79 to 2.7); HR, 2.0 (0.86 to 4.7) All-cause mortality: HR, 1.3 (0.88 to 1.9); HR, 1.4 (0.88 to 2.3)
Bundle Branch Block			
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN codes 7.1, 7.2, 7.4: 1%	CHD death: HR, 1.9 (0.88 to 4.1)*
Dhingra et al, 2006[73] *Framingham Heart Study*	n=1,759 Mean age: 70 yrs (SD, 7) 37% male Mean followup: 12.7 yrs	QRS duration 100-119 ms (incomplete bundle branch block): 17% QRS duration ≥120 ms (complete bundle branch block): 6%	CHF incidence QRS <100 ms: HR, 1 (reference) QRS 100-119 ms: HR, 1.4 (1.0 to 2.0) QRS ≥120 ms: HR, 1.7 (1.3 to 2.4)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities (ARIC) Study* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) Mean followup: 11.6 yrs	MN codes 7.1, 7.2, 7.4: 2%	Nonfatal MI or CHD death: HR, 1.0 (0.67 to 1.6)*
Menotti et al 1997[85] *RIsk Factors and Life Expectancy (RIFLE) Study* Other publications: RIFLE Research Group, 1993[149]	n=22,553 Mean age: NR (50% ages 50-69 yrs) 54% male Mean followup: 6 yrs	MN codes 7.1, 7.2, 7.4: 1.2%	CHD death: RR, 3.3 (1.3 to 8.4) in men*; women not calculated CVD death: RR, 3.6 (1.7 to 7.6) in men; women not calculated All-cause mortality: RR, 1.9 (1.0 to 3.4) in men; RR, 0.79 (0.11 to 5.8) in women
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti et al, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	MN codes 7.1, 7.2, 7.4: 7.3%	CHD death: HR, 1.3 (0.76 to 2.2)*

*Outcome included in meta-analysis.

Abbreviations: CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CVA=cerebral vascular accident; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; LVH=left ventricular hypertrophy; MI=myocardial infarction; MN=Minnesota; NR=not reported; NS=not significant; RR=relative risk; SD=standard deviation; yrs=years.

Table 5. Major and Minor ECG Abnormalities as Predictors of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition or major or minor ECG abnormalities; Prevalence	Risk associated with major or minor ECG abnormalities compared to no abnormalities (95% CI)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	Major ECG abnormality MN codes 4.1, 4.2, 5.1, 5.2, 6.1, 6.2, 7.1, 7.2, 8.1, 8.3: 29% Minor ECG abnormality MN codes 1.3, 2.1, 2.2, 3.1, 3.2, 4.3, 5.3, 9.1: 3.6%	CHD death Major ECG abnormality: HR, 2.3 (1.5-3.7) Minor ECG abnormality: HR, 1.1 (0.77-1.7)
Denes et al, 2007[72] *Women's Health Initiative*	n=14,749 Mean age: 63 yrs (range, 50-79) 0% male Mean followup: 5.2 yrs	Major ECG abnormality Novacodes 1.4, 1.5, 1.7, 1.8, 1.9, 2.3.1, 2.3.2, 2.4, 3.1.0, 3.1.1., 3.2.0, 3.3.0, 3.3.1, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 6.1.1, 1.4, 1.7, 1.8: 6.2% Minor ECG abnormality Novacodes 2.1, 2.2.1, 3.4.1, 3.4.2, 4.1.1, 4.1.2, 5.7, 5.8, 6.1.0, 7.1, 8.1, 10.1, 10.2: 28%	CHD events Major ECG abnormality: HR, 3.0 (2.0-4.5) Minor ECG abnormality: HR, 1.6 (1.1-2.1) CVD events Major ECG abnormality: HR, 2.3 (1.8-3.0) Minor ECG abnormality: HR, 1.4 (1.1-1.7)
Liao et al, 1988[81] *Chicago Heart Association Detection Project in Industry*	n=17,633 Mean age: 51 yrs 55% male Mean followup: 11.5 yrs	Major ECG abnormality MN codes 6.1 or 6.2; 7.1, 7.2, or 7.4; 8.3; 8.1; 4.1; 5.1 or 5.2: 11.1% Minor ECG abnormality MN codes 1.3, 4.3, 5.3, 6.3, 3.1, 3.2, 9.1, 2.1 or 2.2: 6%	CHD death* Major ECG abnormality: HR, 3.7 in men; HR, 1.9 in women Minor ECG abnormality: HR, 2.1 in men; HR, 1.5 in women CVD death* Major ECG abnormality: HR, 3.4 in men; HR, 2.1 in women Minor ECG abnormality: HR, 2.1 in men, HR, 1.5 in women All-cause mortality* Major ECG abnormality: HR, 2.4 in men; HR, 1.4 in women Minor ECG abnormality: HR, 1.7 in men; HR, 1.2 in women
Macfarlane et al, 2007[77] *West of Scotland Coronary Prevention Study (WOSCOPS)*	n=5,835 Mean age: 55 yrs 100% male Mean followup: 4.9 yrs	Minor ECG abnormality MN codes 4.2, 4.3, 5.2, 5.3: 8%	CHD death of nonfatal MI Minor ECG abnormality: HR, 1.7 (1.3-2.3) All-cause mortality Minor ECG abnormality: HR, 2.2 (1.5-3.1)

Table 5. Major and Minor ECG Abnormalities as Predictors of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition or major or minor ECG abnormalities; Prevalence	Risk associated with major or minor ECG abnormalities compared to no abnormalities (95% CI)
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti et al, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	Major ECG abnormality MN codes 1.1, 4.1, 5.1, 6.8, 7.1, 7.4, 8.3: 8% Minor ECG abnormality MN codes 1.2, 1.3, 2.1, 4.2-4, 5.2-5.3, 6.4, 7.2, 7.3, 8.1: 39%	CHD death Major ECG abnormality (vs. absent or marginal abnormality): HR, 3.1 (1.9-5.1) Minor ECG abnormality (vs. absent or marginal abnormality): HR, 1.8 (1.3-2.5)
Sutherland et al, 1993[93] *Charleston Heart Study*	n=993 Mean age: 48 yrs (range, 35-74) 100% male Mean followup: 30 yrs	Major ECG abnormality MN codes 4.1, 4.2, 5.1, 5.2, 7.1, 7.2, 7.4, 8.1, 8.3: 9% Minor ECG abnormality MN codes 1.3, 4.3, 5.3, 6.3, 9.1, 3.1, 2.1, 2.2: 14%	CHD death Major ECG abnormality: HR, 2.7 (1.5-5.0) in white men; HR, 2.0 (0.93-4.1) in black men Minor ECG abnormality: HR, 1.3 (0.74-2.1) in white men; HR, 0.58 (0.24-1.4) in black men All-cause mortality Major ECG abnormality: HR, 2.1 (1.4-3.1) in white men; HR, 1.4 (0.91-2.1) in black men Minor ECG abnormality: HR, 1.2 (0.92-1.7) in white men; HR, 0.79 (0.52-1.2) in black men

*Confidence intervals not reported.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; MI=myocardial infarction; MN=Minnesota; NR=not reported; yrs=years.

Table 6. Other Abnormalities on Resting ECG as Predictors of Cardiovascular Events

Author, year	Sample size Demographics Duration of followup	ECG abnormalities evaluated; Prevalence	Risk associated with abnormality present compared to no abnormality (95% CI)
Crow et al, 2003[68] *Atherosclerosis Risk in Community (ARIC) Study*	n=14,696 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 13 yrs	QTc: continuous variable JTc: continuous variable Wide QRS complex (≥120 ms): 3.1%	Incident MI or CHD death *No wide QRS complex* QTc (per 10 ms): HR, 1.0 (1.0-1.1) in men; 1.1 (1.0-1.2) in women JTc (per 10 ms): HR, 1.0 (1.0-1.1) in men; 1.1 (1.0-1.1) in women *Wide QRS complex* QTc (per 10 ms): HR, 1.1 (0.90-1.2) in men; 1.0 (0.72-1.3) in women JTc (per 10 ms): HR, 1.2 (1.0-1.5) in men; 0.79 (0.56-1.1) in women
Gottdiener et al, 2000[75] *Cardiovascular Heart Study* Other publications: Furberg et al, 1992[147]	n=4,652 (analyzed group with no prevalent CHD) Mean age: 73 yrs (range, 65-100; entire cohort) 40% male Mean followup: 6.3 yrs	Atrial fibrillation: 3.2% Major Q/QS wave: 5.2%	Incident CHF Atrial fibrillation: HR, 1.94 (1.23-3.05) Major Q/QS wave: NS (estimate NR)
Jouven et al, 2005[78] *Paris Prospective Study I*	n=5,713 Mean age: 48 yrs (range, 42-53) 100% male Mean followup: 23 yrs	Resting heart rate >75 bpm: 8.0%	Resting heart rate >75 bpm vs. <60 bpm Sudden death from MI: HR, 3.5 (1.6-7.4) Nonsudden death from MI: HR, 1.6 (0.90-2.7) All-cause mortality: HR, 1.9 (1.6-2.2)
Macfarlane et al, 2007[77] *West of Scotland Coronary Prevention Study (WOSCOPS)*	n=5,835 Mean age: 55 yrs 100% male Mean followup: 4.9 yrs	Right axis deviation: 0.5% High voltage left ventricular lead: 5.1% High voltage right ventricular lead: 0.06% Heart rate Indexed LVM (Rautaharju criteria) Frontal T-axis Positive component of T wave amplitude in lead I Heart rate variability	Nonfatal MI or CHD death Heart rate (10 bpm): HR, 1.13 (1.04-1.24) Indexed LVM (Rautaharju criteria) (per 25 g/m^2): HR, 1.19 (1.03-1.38) Frontal T-axis (per 20°): HR, 0.84 (0.77-0.91) Positive component of T wave amplitude in lead I (per 100 µV): HR, 0.81 (0.72-0.91) Other NS ECG findings in multivariate model: NR All-cause mortality Heart rate variability (per 15 ms): HR, 0.76 (0.67-0.87) Frontal T-axis (per 20°): HR, 0.82 (0.74-0.89) Other NS ECG findings in multivariate model: NR
Machado et al, 2006[82] *Atherosclerosis Risk in Communities Study (ARIC)* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 11.6 yrs	Minor Q wave: 2% Prolonged QTc interval: 9% Major ventricular conduction defect: 2%	Incident CHD (nonfatal MI or CHD death) Minor Q wave: HR, 1.59 (1.08-2.34) Prolonged QTc interval: HR, 1.12 (0.87-1.43) Major ventricular conduction defect: 1.05 (0.67-1.64)

Table 6. Other Abnormalities on Resting ECG as Predictors of Cardiovascular Events

Author, year	Sample size Demographics Duration of followup	ECG abnormalities evaluated; Prevalence	Risk associated with abnormality present compared to no abnormality (95% CI)
Massing et al, 2006[83] *Atherosclerosis Risk in Communities Study (ARIC)*	n=15,070 Mean age: 54 yrs (range, 45-64) 45% male 74% white Mean followup: >10 yrs (11.6 yrs in other ARIC publications)	Ventricular premature contractions: 6.2%	Asymptomatic patients at baseline CHD event: HR, 1.30 (1.06-1.58) CHD death: HR, 2.14 (1.46-3.13) All-cause mortality: HR, 1.48 (1.25-1.75)
Menotti et al, 1997[85] *Risk Factors and Life Expectancy (RIFLE) Study* Other publications: RIFLE Research Group, 1993[149]	n=22,553 Mean age: NR (50% ages 50-69 yrs) 54% male Mean followup: 6 yrs	Q/QS wave High R wave Arrhythmia Any ECG abnormality: 12%	CHD death Q/QS wave: RR, 1.25 (0.29-5.31) in men; RR, 9.88 (1.05-92.6) in women High R wave: RR, 1.62 (0.86-3.05) in men; RR, 5.14 (0.94-28.1) in women Arrhythmia: RR, 2.28 (0.81-6.40) in men; RR, not calculated in women Cardiovascular death Q/QS wave: RR, 2.36 (0.91-6.11) in men; RR, 4.18 (0.51-34.5) in women High R wave: RR, 1.86 (1.13-3.07) in men; RR, 3.66 (0.96-14.0) in women Arrhythmia: RR, 1.58 (0.57-4.38) in men; RR, not calculated in women All-cause mortality Q/QS wave: RR, 1.63 (0.77-3.46) in men; RR, 1.00 (0.13-7.39) in women High R wave: RR, 1.28 (0.89-1.85) in men; RR, 2.17 (0.97-4.85) in women Arrhythmia: RR, 1.92 (1.04-3.54) in men; RR, 0.81 (0.11-5.93) in women
Moller et al, 2007[86] *Uppsala Longitudinal Study of Adult Men*	n=2,322 Age: 50 yrs (all age 50 yrs) 100% male Mean followup: NR (followup >20 yrs with max 32 yrs)	Q/QS wave: 1.3% Atrial fibrillation: 0.3%	Fatal and nonfatal stroke Q/QS wave, atrial fibrillation: NS (estimates NR) Fatal and nonfatal ischemic stroke Atrial fibrillation, followup 0-9.9 yrs: HR, 15 (1.77-128) Atrial fibrillation, followup 0-30, 10-19.9, or 20-30 yrs: NS (estimates NR) Q/QS wave: NS (estimate NR)

Table 6. Other Abnormalities on Resting ECG as Predictors of Cardiovascular Events

Author, year	Sample size Demographics Duration of followup	ECG abnormalities evaluated; Prevalence	Risk associated with abnormality present compared to no abnormality (95% CI)
Rautaharju et al, 2006a and 2006b[89,90] *Women's Health Initiative (WHI)* Other publications: WHI 1998[155]	n=35,715 Mean age: 62 yrs (range, 50-79) 0% male 82% white Mean followup: 6.2 yrs	QRS/T angle STV5 TV1 TV5 QTrr STV5 gradient MI by ECG Cornell voltage R nondipolar voltage Heart rate variability	<u>CHD event</u> T nondipolar voltage (≥13 μV): HR, 1.29 (0.97-1.72) Rest: NS <u>CHD death</u> Cornell voltage (≥1800 μV): HR, 1.91 (1.09-3.36) QTrr (≥437 ms): HR, 2.17 (1.24-3.73) Rest: NS <u>Incident CHF</u> MI by ECG: HR, 1.99 (1.53-2.59) Isolated ST-T abnormality or minor Q wave: HR, 1.55 (1.2-1.99) <u>All-cause mortality</u> MI by ECG: HR, 1.36 (1.10-1.68) Isolated ST-T abnormality or minor Q wave: HR, 1.15 (0.96-1.39)
Rautaharju et al, 2006c[91] *Cardiovascular Health Study*	n=4,085 Mean age: 73 yrs (inclusion criteria age ≥65 yrs) 37% male 85% white and/or other 15% black	QRS/T angle STV5 TV1 TV5 QTrr STV5 gradient MI by ECG Cornell voltage QRS nondipolar voltage Ultrashort heart rate variability	<u>CHD death</u> ST depression: HR, 1.74 (1.28-2.36) MI by ECG, QRS/T angle, QRS nondipolar voltage, LVM by ECG: NS (estimates NR) <u>All-cause mortality</u> Previous MI: HR, 1.50 (1.20-1.87) ST depression: HR, 1.35 (1.14-1.59) LVM by ECG: HR, 1.27 (1.05-1.55) QRS/T angle: HR, 1.18 (0.99-1.40)

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; LVH=left ventricular hypertrophy; LVM=left ventricular mass; MI=myocardial infarction; NR=not reported; NS=not significant; RR=relative risk; yrs=years.

Table 7. Ischemic Changes on Resting ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of ischemic changes Prevalence	Risk associated with ischemic changes compared to no ischemic changes (95% CI)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	MN codes 1.3, 4.1-4.4, 5.1-5.3, 7.1: 10%	CHD death: HR, 1.7 (1.1-2.5)
Menotti et al, 2001[84] *FINE Study* Other publications: Menotti and Seccareccia, 1996[156]	n=1,785 Mean age: NR (range, 65-84 yrs) 100% male Mean followup: 10 yrs	MN codes 1.2 or 1.3, 4.1-4.3, 5.1-5.3: 35%	CHD death: HR, 1.5 (1.1-2.1)

Abbreviations: CHD=coronary heart disease; CI=confidence interval; HR=hazard ratio; ECG=electrocardiography; MN=Minnesota; NR=not reported; yrs=years.

Table 8. Prolonged QT Interval on Resting ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of prolonged QT interval Prevalence	Risk associated with prolonged QT interval compared to no prolonged QT interval (95% CI)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities (ARIC) Study* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) Mean followup: 11.6 yrs	QTc ≥460 ms: 9%	Nonfatal MI or CHD death: HR, 1.1 (0.87-1.4)
Rautaharju et al, 2006a[89] *Women's Health Initiative (WHI)* Other publications: WHI, 1998[155]	n=35,715 Mean age: 62 yrs (range, 50-79) 0% male Mean followup: 6.2 yrs	QTrr ≥437 ms: NR	CHD death: HR, 2.2 (1.2-3.7)

Abbreviations: CHD=coronary heart disease; CI=confidence interval; ECG=electrocardiography; HR=hazard ratio; MI=myocardial infarction; NR=not reported; yrs=years.

Table 9. Estimates of Risk Associated With Resting ECG Abnormalities, Stratified By Sex

Author, year *Study*	Sample Size Demographics Duration of followup	Definition of abnormality Prevalence	Risk associated with abnormality compared to no abnormality in men (95% CI)	Risk associated with abnormality compared to no abnormality in women (95% CI)
Resting ECG				
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	ST segment abnormality, MN codes 4.1-4.3: 2%	CHD death: HR, 3.5 (1.8-6.8)	CHD death: 2.6 (0.99-6.9)
Greenland et al, 2003[76] *Chicago Heart Association Detection Project in Industry*	n=17,615 Mean age: 50 yrs (range, 40-64) 55% male Mean followup: 22 yrs	ST segment abnormality, MN codes 4.3, 4.4: 1.2% in men; 1.5% in women	CHD death: HR, 1.0 (0.66-1.6) CVD death: HR, 0.93 (0.61-1.4) All-cause mortality: HR, 0.95 (0.71-1.3)	CHD death: HR, 1.5 (0.84-2.8) CVD death: HR, 1.5 (0.94-2.5) All-cause mortality: HR, 1.2 (0.87-1.7)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	T wave abnormality, MN codes 5.1-5.3: 8%	CHD death: HR, 2.0 (1.2-3.4)	CHD death: 1.9 (0.89-3.9)
Greenland et al, 2003[76] *Chicago Heart Association Detection Project in Industry*	n=17,615 Mean age: 50 yrs (range, 40-64) 55% male Mean followup: 22 yrs	ST segment or T wave abnormality, MN codes 4.3, 4.4, 5.3, 5.4: 3.6% in men; 5.4% in women	CHD death: HR, 1.4 (0.81-2.3) CVD death: HR, 1.4 (0.90-2.2) All-cause mortality: HR, 1.2 (0.86-1.6)	CHD death: HR, 2.0 (1.2-3.2) CVD death: HR, 1.6 (1.1-2.4) All-cause mortality: HR, 1.3 (0.98-1.7)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	LVH, MN codes 3.1 + 4.1-4.3 or 5.1-5.3: 0.6%	CHD death: HR, 1.8 (0.44-7.6)	CHD death: HR, 1.9 (0.25-14)
Machado et al, 2006[82] *Atherosclerosis Risk in Communities Study (ARIC)* Other publications: ARIC Investigators, 1989[148]	n=12,987 Mean age: 54 yrs (range, 45-64) 43% male Mean followup: 11.6 yrs	LVH, Cornell (men >28 mm; women >22 mm): 2% ST-T strain pattern: MN codes 3.1 or 3.3 + 4.3 or 4.2 or 4.1.1 or 4.1.2 or 5.1 or 5.2 or 5.3: 2%	<u>Nonfatal MI or CHD death</u> ST-T strain pattern: HR, 1.1 (0.50-2.4) in blacks; HR, 6.5 (3.3-13) in whites	<u>Nonfatal MI or CHD death</u> ST-T strain pattern: HR, 2.3 (1.2-4.3) in blacks; HR, 2.8 (0.69-12) in whites
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	Major ECG abnormality (MN codes 4.1, 4.2, 5.1, 5.2, 6.1, 6.2, 7.1, 7.2, 8.1, 8.3): 29% Minor ECG abnormality (MN codes 1.3, 2.1, 2.2, 3.1, 3.2, 4.3, 5.3, 9.1): 3.6%	<u>CHD death</u> Major ECG abnormality: HR, 2.1 (1.2-3.7) Minor ECG abnormality: HR, 0.99 (0.62-1.6)	<u>CHD death</u> Major ECG abnormality: HR, 3.1 (1.4-6.9) Minor ECG abnormality: HR, 1.6 (0.78-3.1)

Table 9. Estimates of Risk Associated With Resting ECG Abnormalities, Stratified By Sex

Author, year *Study*	Sample Size Demographics Duration of followup	Definition of abnormality Prevalence	Risk associated with abnormality compared to no abnormality in men (95% CI)	Risk associated with abnormality compared to no abnormality in women (95% CI)
Liao et al, 1988[81] *Chicago Heart Association Detection Project in Industry*	n=17,633 Mean age: 51 yrs 55% male Mean followup: 11.5 yrs	Major ECG abnormality (MN codes 6.1 or 6.2; 7.1, 7.2, or 7.4; 8.3; 8.1; 4.1; 5.1 or 5.2): 11.1% Minor ECG abnormality (MN codes 1.3, 4.3, 5.3, 6.3, 3.1, 3.2, 9.1, 2.1 or 2.2): 6%	CHD death* Major ECG abnormality: HR, 3.7 Minor ECG abnormality: HR, 2.1 CVD death* Major ECG abnormality: HR, 3.4 Minor ECG abnormality: HR, 2.1 All-cause mortality* Major ECG abnormality: HR, 2.4 Minor ECG abnormality: HR, 1.7	CHD death* Major ECG abnormality: HR, 1.9 Minor ECG abnormality: HR, 1.5 CVD death* Major ECG abnormality: HR, 2.1 Minor ECG abnormality: HR, 1.5 All-cause mortality* Major ECG abnormality: HR, 1.4 Minor ECG abnormality: HR, 1.2
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	Left axis deviation, MN code 2.1: 4.2%	CHD death: HR, 1.5 (0.79-2.7)	CHD death: HR, 1.6 (0.48-5.5)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	Bundle branch block, MN codes 7.1, 7.2, 7.4: 1%	CHD death: HR, 1.8 (0.74-4.6)	CHD death: HR, 2.2 (0.50-10)
Menotti et al, 1997[85] *Risk Factors and Life Expectancy (RIFLE) Study* Other publications: RIFLE Research Group, 1993[149]	n=22,553 Mean age: NR (50% ages 50-69 yrs) 54% male Mean followup: 6 yrs	Bundle branch block, MN codes 7.1, 7.2, 7.4: 1.2%	All-cause mortality: RR, 1.9 (1.0-3.4)	All-cause mortality: RR, 0.79 (0.11-5.8)
Crow et al, 2003[68] *Atherosclerosis Risk in Community (ARIC) Study*	n=14,696 Mean age: 54 yrs (range, 45- 64) 43% male Mean followup: 13 yrs	QTc: continuous variable JTc: continuous variable Wide QRS complex (≥120 ms): 3.1%	Incident MI or CHD death *No wide QRS complex* QTc (per 10 ms): HR, 1.0 (1.0-1.1) JTc (per 10 ms): HR, 1.0 (1.0-1.1) *Wide QRS complex* QTc (per 10 ms): HR, 1.1 (0.90-1.2) JTc (per 10 ms): HR, 1.2 (1.0-1.5)	Incident MI or CHD death *No wide QRS complex* QTc (per 10 ms): HR, 1.1 (1.0-1.2) JTc (per 10 ms): HR, 1.1 (1.0-1.1) *Wide QRS complex* QTc (per 10 ms): HR, 1.0 (0.72-1.3) JTc (per 10 ms): HR, 0.79 (0.56-1.1)
Menotti et al, 1997[85] *Risk Factors and Life Expectancy (RIFLE) Study* Other publications: RIFLE Research Group, 1993[149]	n=22,553 Mean age: NR (50% ages 50-69 yrs) 54% male Mean followup: 6 yrs	Q/QS wave, MN codes 1.1, 1.2, 1.3 ST-T abnormality, MN codes 4.1-4.3 or 5.1-5.3 High R wave, MN codes 3.1, 3.3 Arrhythmia, MN codes 8.1-8.6, 8.9, 9.0, 6.1, 6.2, 6.4 Block, MN codes 7.1, 7.2, 7.4 Any ECG abnormality: 12%	CHD death Q/QS wave: RR, 1.2 (0.29-5.3) High R wave: RR, 1.6 (0.86-3.0) Cardiovascular death Q/QS wave: RR, 2.4 (0.91-6.1) High R wave: RR, 1.9 (1.1-3.1) All-cause mortality Q/QS wave: RR, 1.6 (0.77-3.5) High R wave: RR, 1.3 (0.89-1.8) Arrhythmia: RR, 1.9 (1.0-3.5)	CHD death Q/QS wave: RR, 9.9 (1.0-93) High R wave: RR, 5.1 (0.94-28) Cardiovascular death Q/QS wave: RR, 4.2 (0.51-34) High R wave: RR, 3.7 (0.96-14) All-cause mortality Q/QS wave: RR, 1.0 (0.13-7.4) High R wave: RR, 2.2 (0.97-4.8) Arrhythmia: RR, 0.81 (0.11-5.9)

Table 9. Estimates of Risk Associated With Resting ECG Abnormalities, Stratified By Sex

Author, year *Study*	Sample Size Demographics Duration of followup	Definition of abnormality Prevalence	Risk associated with abnormality compared to no abnormality in men (95% CI)	Risk associated with abnormality compared to no abnormality in women (95% CI)
De Bacquer et al, 1998[71] *Belgian Inter-University Research on Nutrition and Health (BIRNH) Study*	n=9,954 Mean age: 48 yrs (range, 25-74) 52% male Mean followup: 10 yrs	Ischemic changes, MN codes 1.3, 4.1-4.4, 5.1-5.3, 7.1: 10%	CHD death: HR, 1.7 (1.0-2.8)	CHD death: HR, 1.7 (0.81-3.5)

*Confidence intervals not reported.

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; LVH=left ventricular hypertrophy; MI=myocardial infarction; MN=Minnesota; RR=relative risk; yrs=years.

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Adabag et al, 2008[94]	Multiple Risk Factor Intervention Trial (MRFIT) Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=12,555 Mean age: 46 yrs (range, 35-57) 100% male 7% black; other races NR	Failure to reach target heart rate: 19%	25 yrs: CHD death and all-cause mortality 7 yrs: sudden death and fatal/nonfatal MI	Age, sex, smoking, fasting glucose, SBP, HDL, LDL	CHD death (25 yrs): 13% All-cause mortality (25 yrs): 37% 7-yr followup Sudden death: 1.2% Fatal/nonfatal MI: 6.6%	Good
Aktas et al, 2004[95]	Study not named Treadmill/primarily Bruce or modified Bruce protocols United States Self-referred, consecutive adults undergoing routine executive physical	n=3,554 Mean age: 57 yrs (range, 50-75) 81% male 1.8% black; other races NR	ST segment changes: <2 mm, 6%; ≥2 mm, 4.4% Any change: 10.4% Abnormal heart rate recovery: 15.4% (549/3554)	8	Age, sex, smoking, total cholesterol, HDL, SBP, diabetes	All-cause mortality: 3.2% (114/3554)	Fair
Balady et al, 2004[96] Other publications: Framingham Study[150]	Framingham Heart Study Treadmill/standard Bruce protocol United States General community	n=3,043 Mean age: 45 yrs (range, 30-70) 47% male Race NR	ST segment depression: 4.3% Failure to reach target heart rate: 9.0%	18	Age, sex, smoking, diabetes, SBP, DBP, HDL, total cholesterol	Any CHD event (angina, coronary insufficiency, MI, or CHD death): 10%	Good
Blair et al, 1996[97] Other publications: Wei et al, 1999[151]	Aerobics Center Longitudinal Study Treadmill/maximal Balke protocol United States General community	n=32,421 Mean age: 43 yrs (range, 20-88) 79% male Race NR	Abnormal ECG (not defined): 6.8%	8.2 (8.4 in men; 7.5 in women)	Age, sex (results stratified by sex), smoking, SBP, total cholesterol, fasting glucose	CVD death: 0.8% All-cause mortality: 2.1%	Fair
Bodegard et al, 2004[66]	Study not named Bicycle/maximal Norway Work volunteers	n=2,014 Mean age: 50 yrs (range, 40-59) 100% male Race NR	ST segment depression: 14%	22	Age, sex, smoking, SBP, total cholesterol	CHD death: 15% All-cause mortality: 37% Acute MI: 19% Coronary artery bypass graft surgery: 6.0% Stroke: 7.7%	Good

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Cole et al, 2000[98]	Lipid Research Clinics Prevalence Study Treadmill/standard or modified Bruce protocol United States General population	n=5,234 Mean age: 44 yrs 61% male 96% white (other races NR)	Heart rate recovery at 2 minutes <42 bpm: 33%	12	Age, sex, SBP, smoking, diabetes, lipid profiles (cholesterol)	CVD death: 2.2% All-cause mortality: 6.2%	Good
Cournot et al, 2006[99]	Study not named Exercise method not described/submaximal France Cardiology clinic attendees	n=1,051 Mean age: 52 yrs (range, 18-79) 64% male Race NR	ST segment depression: 5.3%	6	Age, sex, smoking, diabetes, SBP, HDL, total cholesterol	CHD or CVD death: 0.6% Any coronary event (cardiac death, sudden death, MI, angina): 3.2% All-cause mortality: 1.7% CHD or CVD death: 0.6% Stable or unstable angina: 1.2% Nonfatal MI: 1.4%	Good
Ekelund et al, 1989[100]	Lipid Research Clinics Coronary Primary Prevention Trial Treadmill/submaximal Bruce protocol United States Clinical trial enrollees	n=3,775 Mean age: 47 yrs (range, 35-59) 100% male Race NR	ST segment depression or elevation: 8.2%	7.4	Age, sex, smoking, diabetes, SBP, HDL, LDL	CHD death: 1.8% Nonfatal MI: 7.6% All-cause mortality: 3.7%	Good
Fleg et al, 1990[101]	Baltimore Longitudinal Study of Aging Treadmill/modified Balke protocol United States General community	n=407 Mean age: 60 yrs (range, ≥40 yrs) 71% male 97% white	ST segment depression: 16%	4.6	Age, sex, smoking, diabetes, hypertension, total cholesterol	CVD death: 1.7% Nonfatal MI: 3.2% Angina: 4.9% Any coronary event: 9.8%	Good
Giagnoni et al, 1983[102]	Study not named Supine ergometer/sub-maximal Italy Factory workers	n=514 Age: 44% ages 46-65 yrs (range, 18-65) 73% male Race NR	ST segment depression: 1.2%	6.0	Age, sex, smoking, SBP, total cholesterol	Any coronary event (angina, MI, sudden death): 6.6% All-cause mortality: 3.1%	Good

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Gordon et al, 1986[103]	Lipid Research Clinics Mortality Follow-Up Study Treadmill/submaximal modified Bruce protocol United States Lipid clinic attendees	n=3,640 Age: 35% ages 50-79 yrs (range, 30-79) 100% male 100% white	ST segment depression or elevation: 18%	8.1	Age, sex (100% male), smoking, hyperglycemia, hypertension, HDL, LDL	CHD death: 1.4% CVD death: 1.8% All-cause mortality: 4.1%	Fair
Gulati et al, 2003[105]	St James Women Take Heart Treadmill/maximal Bruce protocol United States General community	n=5,271 Mean age: 52 yrs (range NR [SD, 11]) 0% male 86% white	Mean exercise capacity: 8.0 METs	8.4	Age, sex (100% female), smoking, SBP, DBP, HDL, total cholesterol	All-cause mortality: 3.2%	Fair
Gulati et al, 2005[104] Same population as Gulati et al, 2003[105]	St James Women Take Heart Treadmill/maximal Bruce protocol United States General community	n=5,636 Mean age: 52 yrs (range NR [SD, 11]) 0% male 86% white	Mean Duke treadmill score: 8	9	Age, sex, smoking, diabetes, SBP, DBP, HDL, total cholesterol	CHD death: 0.9% All-cause mortality: 3.0%	Good
Josephson et al, 1990[106]	Baltimore Longitudinal Study of Aging Treadmill/submaximal modified Balke protocol United States General population	n=726 Mean age: 55 yrs (range, 22-84) 63-87% male (varied by group) Race NR	ST segment depression: 12% on initial test; 13% on followup test	6.4-7.7	Age, sex, smoking, hypertension, cholesterol	Cardiac events (angina, nonfatal MI, cardiac death): 8.8%	Fair
Jouven et al, 2000[107] Other publications: Filipovsky et al, 1992[152]	Paris Protective Study Bicycle/standardized graded exercise test France Civil servants	n=6,101 Mean age: 48 yrs (range, 42-52) 100% male Race NR	ST segment depression: 4.4% Frequent premature ventricular contractions: 2.8%	23	Age, sex (100% male), smoking, diabetes, SBP, total cholesterol	CHD death: 7.1% All-cause mortality: 27%	Good
Jouven et al, 2005[78]	Paris Protective Study I Bicycle/standardized graded exercise test France Civil servants	n=5,713 Mean age: 48 yrs (range, 42-53) 100% male Race NR	Abnormal (<89 bpm) heart rate increase during exercise: 8% Abnormal heart rate recovery (decrease of <25 bpm at 1 min after cessation): 6%	23	Age, sex (100% male), smoking, diabetes, SBP, cholesterol	Fatal MI (sudden death): 1.4% Fatal MI (nonsudden death): 2.3% All-cause mortality: 27%	Good

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Kurl et al, 2003[108]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,726 Mean age: 52 yrs (range, 42-60) 100% male Race NR	ST segment depression: 7.1%	10	Age, sex (100% male), smoking, diabetes, SBP, LDL	CHD death: 5.0% Stroke: 4.2%	Fair
Kurl et al, 2009[109]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,639 Mean age: 52 yrs (range, 42-60) 100% male Race NR	ST segment depression: 6.7%	16	Age, sex, smoking, diabetes, SBP, HDL, total cholesterol	Stroke: 5.9%	Fair
Lauer et al, 1996[110]	Framingham Offspring Study Treadmill/submaximal Bruce protocol United States Offspring and spouses of Framingham Heart Study participants	n=1,575 Mean age: 43 yrs (range NR) 100% male Race NR	Failure to reach target heart rate: 21% Increase in heart rate from rest to peak exercise: continuous outcome Ratio of heart rate to metabolic reserve used by stage 2 (7.1 METs) of exercise: continuous outcome	7.7	Age, sex, smoking, hypertension, diabetes, cholesterol	CHD events (MI, angina, sudden cardiac death): 6.0% All-cause mortality: 3.5%	Fair
Laukkanen et al, 2001[111]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,769 Mean age: 52 yrs (range, 42-60) 100% male Race NR	ST segment depression during exercise: 10.7% After exercise: 3.1%	10	Age, sex (100% male), smoking, SBP, diabetes, LDL, HDL	CHD death: 3.0% CVD death: 4.4% Nonfatal coronary events (MI or typical angina): 9.8%	Good
Laukkanen et al, 2006[112]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,596 Mean age: 52 yrs (range, 42-61) 100% male Race NR	Peak oxygen pulse (VO_2 max/maximum heart beat): continuous variable ST segment depression: 6.8%	14	Age, sex (100% male), smoking, diabetes, SBP, DBP, HDL, LDL	CHD death: 4.2% All-cause mortality: 17%	Good

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Laukkanen et al, 2008[113]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle ergometer/maximal symptom-limited exercise test Finland General population	n=1,639 Mean age: 52 yrs (range, 42-60) 100% male Race NR	Exercise capacity (highest workload achieved during test): continuous outcome; also grouped into quartiles (>230 W; 196-230 W; 162-195 W; <162 W) Exercise-induced ST depression (horizontal or downsloping ST depression 1.0 mm 80 ms from J-point): 6.5%	16.6	Age, sex (100% male), smoking, diabetes, SBP, DBP, total cholesterol, HDL (Framingham risk score) or age, sex (100% male), total cholesterol, SBP, smoking (European SCORE)	CVD death: 7.1% Major CVD event: 21% All-cause mortality: 19%	Good
Lyerly et al, 2008[114]	Aerobics Center Longitudinal Study Treadmill/maximal modified Balke protocol United States General population (subgroup of persons with diabetes)	n=2,854 Mean age: 50 yrs (range, 21-84) 100% male Race NR	ST segment depression or elevation ≥1 mm ≥0.08 s from J-point: 11% ST segment depression 0.5-1.0 mm ≥0.08 s: 11%	16	Age, sex (100% male), smoking, fasting glucose, hypertension, hypercholesterolemia	CHD death: 11% CVD death: 7.4% All-cause mortality: 15%	Fair
Lyerly et al, 2009[115]	Aerobic Center Longitudinal Study Treadmill/maximal United States Impaired fasting glucose or undiagnosed diabetes mellitus population	n=3,044 Mean age: 47.4 yrs (range, 20-79) 100% female Mostly white (details NR)	Cardiorespiratory fitness Low: 17% (517/ 3044) Moderate: 34% (1041/3044) High: 49% (1486/ 3044)	15.6	Age, sex (100% female), smoking, alcohol use, hypertension, hypercholesterolemia, family history of diabetes	CVD death: 1.6% All-cause mortality: 5.6%	Fair
Mora et al, 2003[116]	Lipid Research Clinics Prevalence Study Treadmill/maximal Bruce protocol United States General population	n=2,994 Mean age: 47 yrs 100% female 94% white (other races NR)	ST segment depression: 37% Ventricular pre-mature contractions or tachycardia: 7.6% Failure to reach target heart rate: 37%	20.3	Age, sex (100% female), smoking, diabetes, LDL, HDL, hypertension	CVD death: 4.9% All-cause mortality: 14%	Good

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Mora et al, 2005[117]	Lipid Research Clinics Prevalence Study Treadmill/standard Bruce protocol United States General population	n=6,126 Mean age: 45 yrs (SD, 10; range NR) 54% male 96% white; other races NR	Heart rate recovery and exercise capacity (based on sex-specific medians) High + high: 28% Either low: 41% Low + low: 31%	20	Age, sex, smoking, total cholesterol, HDL, hypertension	10-yr followup, CVD death: 1.3% 20-yr followup, CVD death: 4%	Fair
Morshedi-Meibodi et al, 2002[118]	Framingham Offspring Study Treadmill/Bruce protocol United States General population	n=2,967 Mean age: 43 yrs (range NR [SD, 10]) 47% male Race NR	Heart rate recovery: continuous variable Heart rate recovery at 1 min <12 bpm: NR Heart rate recovery at 2 min <42 bpm: NR	15	Age, sex, smoking, diabetes, SBP, DBP, HDL, total cholesterol	CHD events: 7.2% CVD events: 10% All-cause mortality: 5.6%	Fair
Okin et al, 1991[119]	Framingham Offspring Study Treadmill/standard Bruce protocol United States General population	n=3,168 Mean age: 44 yrs (rage, 17-70 [SD, 10]) 48% male Race NR	Heart rate adjusted ST segment depression index ≥1.6 µV bpm: 8.7% Abnormal rate-recovery loop: 6.0%	4.3	Age, sex, smoking, diabetes (fasting blood glucose), hypertension (DBP), total cholesterol	CHD events (angina, ischemic chest pain, fatal/nonfatal MI, sudden/nonsudden coronary death): 2.1% (65/3168)	Good
Okin et al, 1996[120]	Multiple Risk Factor Intervention Trial Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=5,940 Mean age: NR (range, 35-57 yrs) 100% male Race NR	ST segment depression: 3.1% Heart rate adjusted ST segment depression index ≥1.60 µV bpm: 12%	7	Age, sex (100% male), DBP, total cholesterol, smoking	CHD death: 1.8% (109/5940)	Fair
Peters et al, 1983[121]	Study not named Bicycle ergometer/20-min heart-rate-controlled graded exercise test United States Men employed in fire or law enforcement departments	n=2,779 Median age: 41 yrs (mean NR; range, 35-53) 100% male Race NR	Low physical work capacity, defined as <median for each age group (median for entire cohort, 140 W)	4.8	Age, sex (100% male), total cholesterol, smoking, hypertension	Fatal MI: 0.2% Nonfatal MI: 1.1%	Fair

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
Rautaharju et al, 1986[122]	Multiple Risk Factor Intervention Trial Treadmill/standard Bruce protocol United States Clinical trial enrollees	n=6,150 Mean age: 46 yrs (range, 35-57) 100% male 93% white 7% black	ST segment depression: 12%	7	Age, sex (100% male), smoking, DBP, total cholesterol	CHD death: 1.8% CVD death: 2.1% All-cause mortality: 3.8% Silent MI: 2.4% Clinical MI: 3.5%	Good
Rutter et al, 2002[123] Other publications: Rutter et al, 1999[153]	Study not named Treadmill United Kingdom Diabetes clinic patients	n=86 Mean age: 62 yrs (range, 45-75) 72% male Race NR	ST segment depression (>1 mm horizontal or down-sloping ST-segment depression 80 ms after J-point for 3 cons. beats): 52%	2.8	Age, sex, smoking, hemoglobin A1c, clinic + 24-hr ambulatory BP, total cholesterol (Framingham risk score separate variable)	Any CHD event (cardiac death, MI, new-onset angina): 17%	Fair
Rywik et al, 1998[124]	Baltimore Longitudinal Study of Aging Treadmill/submaximal modified Balke protocol United States General population	n=825 Mean age: 51 yrs (range, 22-89) 60% male Race NR	ST segment depression: 18% during exercise; 7.6% during recovery	9	Age, sex, smoking, cholesterol, hypertension, diabetes (fasting glucose)	Coronary events (angina, MI, coronary death): 6.7% (55/825)	Good
Rywik et al, 2002[125]	Baltimore Longitudinal Study of Aging Treadmill/modified Balke protocol United States General population volunteers	n=1,083 Mean age: 52 yrs (SD, 18) 57% male Race NR	≥1 mm horizontal or downsloping ST segment depression (MN code 11.1):16% 0.5-1 or ≥1 mm horizontal or down-sloping ST segment depression (MN codes 11.2, 11.1); <0.5 mm down-sloping ST segment depression or T nadir <0.5 mm below baseline (MN code 11.3); or ST segment depression <0.5 mm at rest or induced by postural shift/hyper-ventilation, worsened to MN code 11.1 during/after test:44%	7.9	Age, sex, total cholesterol, glucose, hypertension	Any coronary event: 7% Specific events- Angina: 3% MI: 2% CHD death: 2%	Fair

Table 10. Cohort Studies of Exercise ECG Abnormalities as Predictors of Cardiovascular Events

Author, year	Study name Exercise test Country Population	Sample size Demographics	Exercise ECG abnormality Prevalence	Mean followup (yrs)	Framingham risk factor adjusted	All-cause mortality and incident cardio-vascular events	Quality
			Duration of exercise: continuous variable				
Savonen et al, 2007[126]	Kuopio Ischemic Heart Disease Risk Factor Study Bicycle/maximal symptom-limited exercise test Finland General population	n=1,314 Mean age: 52 yrs (range, 42-61) 100% male Race NR	ST segment depression: 14% Workload (chrono-tropic index at heart rate of 100 bpm): continuous variable	12	Age, sex (100% male), smoking, diabetes, SBP, DBP, HDL, LDL	CHD death: 2.7% CVD death: 3.9% All-cause mortality: 10%	Fair
Siscovick et al, 1991[127] Other publications: Lipid Research Clinics Program 1984[154]	Lipid Research Clinics Coronary Primary Prevention Trial Treadmill/submaximal Bruce protocol United States Men with hypercholesterolemia	n=3,617 Mean age: NR (range, 35-59 yrs) 100% male 100% white	ST depression or elevation ≥1 mm or 10 µV-s	7.4	Age, sex (100% male), LDL, HDL, smoking, SBP	Acute cardiac event (nonfatal MI and CHD death): 1.8% (51/2893)	Good
Slattery et al, 1988[128]	US Railroad Study Treadmill/submaximal 3-mine exercise test United States Men employed in US railroad industry	n=2,431 Mean age: NR (range, 22-79 yrs) 100% male 100% white	Heart rate following 3-min submaximal exercise test, categorized into quartiles	NR (max duration, 20 yrs)	Age, sex (100% male), SBP, total cholesterol, smoking	CHD death: 11% All-cause mortality: 27%	Fair
Sui et al, 2007[129]	Aerobics Center Longitudinal Study Treadmill/modified Balke protocol United States General population	n=26,637 Mean age: NR (range, 18-83 yrs) 78% male Race NR	Fitness level, based on duration of maximal treadmill exercise test Low: lowest quintile Moderate: 2nd and 3rd quintiles High: upper 2 quintiles	10	Age, smoking, hypertension, diabetes, dyslipidemia	Any CVD event (MI, revascularization, stroke): 5.7% MI: 1.8% Revascularization: 2.8% Stroke: 1.1%	Fair

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CVD=cardiovascular disease; DBP=diastolic blood pressure; ECG=electrocardiography; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LVH=left ventricle hypertrophy; METs=metabolic equivalents; MI=myocardial infarction; MN=Minnesota; NR=not reported; SBP=systolic blood pressure; SD=standard deviation; yrs=years.

Table 11. ST Segment Changes on Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of exercise-induced ST depression Prevalence	Risk associated with exercise-induced ST depression compared to no ST depression (95% CI)
Aktas, 2004[95] *Study not named*	n=3,554 Mean age: 57 yrs (range, 50-75) 81% male Mean followup: 8 yrs	1 to <2 mm horizontal or downsloping ST segment depression at 80 ms after the J-point: 6.0% ≥2 mm: 4.4% Any depression: 10.4%	All-cause mortality ST segment depression 1 to <2 mm: HR, 1.0 (0.57-1.9)* ≥2 mm: HR, 0.86 (0.32-2.3)
Balady et al, 2004[96] *Framingham Heart Study*	n=3,043 Mean age: 45 yrs (range, 30-70) 47% male Mean followup: 18 yrs	≥1 mm horizontal or downsloping ST segment depression in 3 consecutive beats: 4.3%	Any CHD event*: HR, 1.8 (1.2-2.9) in men; HR, 1.9 (0.91-4.0) in women
Bodegard et al, 2004[66] *Study not named*	n=2,014 Mean age: 50 yrs (range, 40-59) 100% male Mean followup: 22 yrs	≥0.50 mm ST segment depression in 3 consecutive beats: 14%	CHD death: HR, 1.5 (1.1-2.0)*
Cournot et al, 2006[99] *Study not named*	n=1,051 Mean age: 52 yrs (range, 18-79) 64% male Mean followup: 6 yrs	≥1.0 mm ST segment depression at 80 ms after the J-point in at least 2 leads: 5.3%	Any coronary event (cardiac death, sudden death, MI, or angina) Adjusted for risk factors: HR, 2.3 (0.87-5.6) Adjusted for 10-yr Framingham risk: HR, 2.1 (0.86-5.0)*
Ekelund et al, 1989[100] *Lipid Research Clinics Coronary Primary Prevention Trial*	n=3,775 Mean age: 47 yrs (range, 35-59) 100% male Mean followup: 7.4 yrs	ST segment depression or elevation ≥1 mm; ST integral decreased by ≥10 µV-s from rest or to negative if positive at rest; ST integral increased by ≥10 µV-s from rest: 8.2%	CHD death: HR, 5.7 (2.7-12)* Nonfatal MI: HR, 1.2 (0.7-2.1) All-cause mortality: HR, 3.3 (1.8-5.9)
Fleg et al, 1990[101] *Baltimore Longitudinal Study of Aging*	n=407 Mean age: 60 yrs (range, ≥40) 71% male Mean followup: 4.6 yrs	≥1 mm horizontal or downsloping ST segment depression (MN code 11.1): 16%	Any coronary event: HR, NS (data NR) when adjusted for traditional risk factors; HR, 2.4 (CI NR) when also adjusted for duration of ETT and percentage of age-predicted maximal heart rate
Giagnoni et al, 1983[102] *Study not named*	n=514 Mean age: 44% ages 46-65 yrs (range, 18-65) 73% male Mean followup: 6.0 yrs	≥1 mm horizontal or downsloping ST segment depression (MN code 11.1): 1.2%	Any coronary event: HR, 4.5 (2.3-8.8)* All-cause mortality: HR, 1.25 (0.39-3.99)
Gordon et al, 1986[103] *Lipid Research Clinics Mortality Follow-up*	n=3,640 Mean age: 35% ages 50-79 yrs (range, 30-79) 100% male Mean followup: 8.1 yrs	≥1 mm ST depression or elevation (with ST integral criteria): 18%	CVD death: HR, 4.2 (2.0-8.9)* All-cause mortality: HR, 3.4 (2.0-5.8)
Josephson et al, 1990[106] *Baltimore Longitudinal Study of Aging*	n=726 Mean age: 55 yrs (range, 22-84) 63-87% male (varied by group) Mean followup: 6.4-7.7 yrs	≥1 mm flat or downsloping ST segment depression 0.08 s after the J-point in the majority of complexes: 12% on initial test, 13% on followup test	Cardiac events (angina, nonfatal MI, cardiac death) ST segment depression on initial test vs. no ST segment depression: HR, 2.7 (1.4-5.3) ST segment depression on followup test vs. no ST segment depression: HR, 2.8 (1.4-5.4)

Table 11. ST Segment Changes on Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of exercise-induced ST depression Prevalence	Risk associated with exercise-induced ST depression compared to no ST depression (95% CI)
Jouven et al 2000[107] *Paris Protective Study* Other publications: Filipovsky et al, 1992[152]	n=6,101 Mean age: 48 yrs (range, 42-52) 100% male Mean followup: 23 yrs	J-point depression of ≥1 mm with flat or downsloping ST segment either during exercise or recovery: 4.4%	CVD death: HR, 2.6 (1.9-3.6)*
Kurl et al, 2003[108] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,726 Mean age: 52 yrs (range, 42-60) 100% male Mean followup: 10 yrs	Horizontal or downsloping ST segment depression ≥1.0 mm at 80 ms after the J-point or any ST-segment depression >1.0 mm at 80 ms after the J-point: 7.1%	CHD death: HR, 3.5 (2.0-6.0) Stroke: HR, 2.2 (1.1-4.3)
Kurl et al, 2009[109] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,639 Mean age: 52 yrs (range, 42-60) 100% male Mean followup: 16 yrs	Horizontal or downsloping ST segment depression ≥1.0 mm at 80 ms after J-point or any ST segment depression of >1.0 mm at 80 ms after J-point: 6.7%	All stroke: HR, 1.6 (0.80-3.4) Ischemic stroke: HR, 1.7 (0.74-3.9)
Laukkanen et al, 2001[111] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,769 Mean age: 52 yrs (range, 42-60) 100% male Mean followup: 10 yrs	Horizontal or downsloping ST depression ≥1 mm 80 ms after the J-point or any ST depression of >1 mm at 80 ms after the J-point: 11% during exercise; 3.1% during recovery	<u>ST depression during exercise</u> CHD death: HR, 3.5 (1.9-6.5) CVD death: HR, 3.3 (1.9-5.5) Acute coronary event: HR, 1.7 (1.1-2.6) <u>ST depression during recovery</u> CHD death: HR, 4.7 (2.1-11) CVD death: HR, 3.7 (1.8-7.5) Acute coronary event: HR, 2.3 (1.3-4.2)
Laukkanen et al, 2008[113] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,639 Mean age: 52 yrs (range, 42-60) 100% male Mean followup: 16.6 yrs	Horizontal or downsloping ST depression 1.0 mm 80 ms after the J-point: 6.5%	CVD death: HR, 2.1 (1.1-3.8)* Major CVD events (first fatal or nonfatal coronary or cerebrovascular event): HR, 1.4 (0.91-2.1) All-cause mortality: HR, 1.4 (0.89-2.1)
Mora et al, 2003[116] *Lipid Research Clinics Prevalence Study*	n=2,994 Mean age: 46 yrs (range NR) 100% female Mean followup: 20.3 yrs	≥1 mm horizontal or downsloping ST segment depression 0.08 s after the J-point in the last stage or exercise or recovery	CVD death: HR, 0.88 (0.48-1.6)* All-cause mortality: 0.69 (0.45-1.0)
Okin et al, 1996[120] *Multiple Risk Factor Intervention Trial*	n=5,940 Mean age: NR (range, 35-57 yrs) 100% male Mean followup: 7 yrs	ST segment depression: 3.1% Heart rate adjusted ST segment depression index ≥1.60 µV bpm: 12%	<u>CHD death</u> ST segment depression: HR, 1.4 (0.60-3.5)* Abnormal heart rate adjusted ST segment depression index: HR, 3.6 (2.4-5.4)
Rautaharju et al, 1986[122] *Multiple Risk Factor Intervention Trial*	n=6,150 Mean age: 46 yrs (range, 35-57), based on entire cohort 100% male Mean followup: 7 yrs	ST segment depression ≥16 µV-s in leads CS5, aVL, aVF, or V5 during or after exercise (in ECG with <6 µV-s ST segment depression at rest): 12%	CHD death: HR, 3.4 (p<0.05; CI NR) CVD death: HR, 3.0 (p<0.01; CI NR) All-cause mortality: HR, 1.6 (p<0.01; CI NR) Clinical MI: HR, 1.7 (p<0.05; CI NR)

Table 11. ST Segment Changes on Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Definition of exercise-induced ST depression Prevalence	Risk associated with exercise-induced ST depression compared to no ST depression (95% CI)
Rywik et al, 1998[124] *Baltimore Longitudinal Study of Aging*	n=825 Mean age: 51 yrs (range, 22-89) 60% male Mean followup: 9 yrs	≥1 mm J-point depression with ST segment flat or downsloping in the majority of complexes in any ECG lead except AVR (MN code 4.1): 18% during exercise; 7.6% during recovery	Coronary events (angina, nonfatal MI, CHD death) ST segment depression during exercise vs. no ST segment depression: OR, 2.6 (1.3-5.2) ST segment depression during recovery vs. no ST segment depression: OR, 2.4 (1.0-5.5)
Rywik et al, 2002[125] *Baltimore Longitudinal Study of Aging*	n=1,083 Mean age: 52 yrs (SD, 18) (range NR) 57% male Mean followup: 7.9 yrs	≥1 mm horizontal or downsloping ST segment depression (MN code 11.1): 16%	Coronary events (angina, nonfatal MI, CHD death): HR, 2.7 (1.6-4.7)*
Savonen et al, 2007[126] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,314 Mean age: 52 yrs (range, 42-61) 100% male Mean followup: 12 yrs	Horizontal or downsloping ST segment depression ≥0.5 mm at 80 ms after the J point: 13.9%	CHD death: HR, 4.3 (2.2-8.5) CVD death: HR, 3.1 (1.8-5.6) All-cause mortality: NS (data NR)
Siscovick et al, 1991[127] *Lipid Research Clinics Coronary Primary Prevention Trial*	n=3,617 Mean age: NR (range, 35-59 yrs) 100% male Mean followup: 7.4 yrs	ST segment depression or elevation ≥1 mm or 10 μV-s	Definite CHD death during activity: RR, 8.0 (1.5-42.4) Acute cardiac events (nonfatal MI and CHD death): RR, 2.6 (1.3-5.2) Definite nonfatal MI: RR, 1.7 (0.7-4.1)

*Outcome included in meta-analysis.

Abbreviations: AVR=aortic valve replacement; bpm=beats per minute; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; ETT=exercise treadmill test; HR=hazard ratio; MI=myocardial infarction; MN=Minnesota; NR=not reported; NS=not significant; OR=odds ratio; RR=relative risk; SD=standard deviation; yrs=years.

Table 12. Chronotropic Incompetence, Heart Rate Recovery, and Ventricular Ectopy During Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Exercise ECG abnormality Prevalence	Effect Size of ECG abnormality compared to no abnormality (95% CI)
Chronotropic Incompetence			
Adabag et al, 2008[94] *Multiple Risk Factor Intervention Trial*	n=12,555 Mean age: 46 yrs (range, 35-57) 100% male Mean followup: 7 or 25 yrs (varied by outcome)	Failure to reach 85% of predicted maximum heart rate: 19%	CHD death (25 yrs): HR, 1.4 (1.2-1.5)* All-cause mortality (25 yrs): HR, 1.3 (1.2-1.4) Sudden death (7 yrs): HR, 1.8 (1.3-2.6) Fatal or nonfatal MI (7 yrs): HR, 1.3 (1.1-1.5)
Balady et al, 2004[96] *Framingham Heart Study* Other publications: Framingham Study[150]	n=3,043 Mean age: 45 yrs (range, 30-70) 47% male Mean followup: 18 yrs	Failure to reach 85% of predicted maximum heart rate: 9.0%	Any CHD event: HR, 1.6 (1.2-2.2)*
Bodegard et al, 2004[66] *Study not named*	n=2,014 Mean age: 50 yrs (range, 40-59) 100% male Mean followup: 22 yrs	Maximum heart rate: continuous variable	CHD death (per 1 SD maximum heart rate [13.3 bpm]): RR, 0.75 (0.66-0.85)
Jouven et al, 2005[78] *Paris Prospective Study I*	n=5,713 Mean age: 48 yrs (range, 42-53) 100% male Mean followup: 23 yrs	Heart rate increase <89 bpm during exercise: 8.3%	Heart rate increase <89 vs. >113 bpm during exercise Sudden death from MI: HR, 4.0 (1.5-11) Nonsudden death from MI: HR, 1.2 (0.62-2.2) All-cause mortality: 1.5 (1.3-1.8)
Lauer et al, 1996[110] *Framingham Offspring Study*	n=1,575 Mean age: 43 yrs (range NR) 100% male Mean followup: 7.7 yrs	Failure to reach 85% of predicted maximum heart rate: 21% Increase in heart rate from rest to peak exercise: continuous outcome Ratio of heart rate to metabolic reserve used by stage 2 (7.1 METs) of exercise: continuous outcome	Failure to reach target heart rate CHD events (MI, angina, sudden cardiac death): HR, 1.8 (1.1-2.7)* All-cause mortality: HR, 1.1 (0.59-1.9) Increase in heart rate from rest to peak exercise (per 1 SD decrease [12 bpm]) CHD events: HR, 1.3 (1.1-1.5) All-cause mortality: HR, 1.2 (1.0-1.5) Ratio of heart rate to metabolic reserve used by stage 2 of exercise (per 1 SD decrease [0.20]) CHD events: HR, 1.4 (1.1-1.6) All-cause mortality: HR, 1.3 (1.0-1.6)
Mora et al, 2003[116] *Lipid Research Clinics Prevalence Study*	n=2,994 Mean age: 46 yrs 100% female Mean followup: 20.3 yrs	Failure to reach 90% of predicted maximum heart rate: 37%	CVD death: HR, 1.4 (1.0-2.1) All-cause mortality: HR, 1.2 (1.0-1.5)
Slattery et al, 1988[128] *U.S. Railroad Study*	n=2,431 Mean age: NR (range, 22-79 yrs) 100% male Mean followup: NR (max 20 yrs)	Heart rate following 3-min sub-maximal exercise test >127 bpm: 22%	Submaximal exercise heart rate 105 vs. 135 bpm CHD death: HR, 1.2 (1.1-1.3) All-cause mortality: HR, 1.4 (1.3-1.5)

Table 12. Chronotropic Incompetence, Heart Rate Recovery, and Ventricular Ectopy During Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Exercise ECG abnormality Prevalence	Effect Size of ECG abnormality compared to no abnormality (95% CI)
Heart Rate Recovery			
Aktas et al, 2004[95] *Study not named*	n=3,554 Mean age: 57 yrs (range, 50-75) 81% male 1.8% black (other races NR) Mean followup: 8 yrs	Abnormal heart rate recovery (decrease of <12 beats during first minute following exercise): 15% (549/3554)	All-cause mortality: HR, 1.6 (1.0-2.4)*
Cole et al, 2000[98] *Lipid Research Clinics Prevalence Study*	n=5,234 Mean age: 44 yrs 61% male 96% white (other races NR) Mean followup: 12 yrs	Abnormal heart rate recovery at 2 min (change in heart rate from peak to 2 minutes into recovery ≤42 bpm): 33%	All-cause mortality: HR, 1.6 (1.2-2.0)* CVD death: HR, 2.0 (1.1-3.4)
Jouven et al, 2005[78] *Paris Prospective Study I*	n=5,713 Mean age: 48 yrs (range, 42-53) 100% male Mean followup: 23 yrs	Decrease in heart rate 1 min after cessation of exercise <25 bpm: 5.6%	Decrease in heart rate 1 min after cessation of exercise <25 vs. >40 bpm Sudden death from MI: HR, 2.1 (0.92-4.6) Nonsudden death from MI: HR, 0.93 (0.41-1.7) All-cause mortality: HR, 1.3 (1.1-1.5)
Morshedi-Meibodi et al, 2002[118] *Framingham Offspring Study*	n=2,967 Mean age: 43 yrs (range NR [SD, 10]) 47% male Mean followup: 15 yrs	Heart rate recovery index (change in heart rate during 1 min recovery from exercise): continuous variable Abnormal heart rate recovery at 1 min (change in heart rate from peak to 1 minute into recovery <12 bpm): NR Abnormal heart rate recovery at 2 min (change in heart rate from peak to 2 minutes into recovery <42 bpm): NR	CHD event Heart rate recovery index, per ΔHR_{1min}: HR, 0.94 (0.83-1.1) Abnormal heart rate recovery at 1 min: HR, 1.1 (0.65-1.8) Abnormal heart rate recovery at 2 min: HR, 1.1 (0.81-1.5) CVD event Heart rate recovery index, per ΔHR_{1min}: HR, 0.94 (0.84-1.1) Abnormal heart rate recovery at 1 min: HR, 1.0 (0.66-1.5) Abnormal heart rate recovery at 2 min: HR, 1.2 (0.90-1.5) All-cause mortality Heart rate recovery index, per ΔHR_{1min}: HR, 1.1 (0.93-1.2) Abnormal heart rate recovery at 1 min: HR, 1.2 (0.71-2.1)* Abnormal heart rate recovery at 2 min: HR, 0.75 (0.52-1.1)

Table 12. Chronotropic Incompetence, Heart Rate Recovery, and Ventricular Ectopy During Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Exercise ECG abnormality Prevalence	Effect Size of ECG abnormality compared to no abnormality (95% CI)
Ventricular Ectopy			
Jouven et al, 2000[107] *Paris Protective Study* Other publications: Filipovsky et al, 1992[152]	n=6,101 Mean age: 48 yrs (range, 42-52) 100% male Mean followup: 23 yrs	Run of ≥2 consecutive PVD or PVD totaling >10% of all VD on ECG: 2.8%	CVD death: RR, 2.5 (1.6-3.9)
Mora et al, 2003[116] *Lipid Research Clinics Prevalence Study*	n=2,994 Mean age: 46 yrs 100% female Mean followup: 20.3 yrs	Multifocal or ≥10% PVD in last stage of exercise or recovery, or test terminated due to ventricular tachycardia: 7.6%	CVD death: HR, 1.7 (1.1-2.6) All-cause mortality: HR, 1.2 (0.90-1.6)

*Outcome included in meta-analysis.

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; METs=metabolic equivalents; MI=myocardial infarction; NR=not reported; PVD=premature ventricular depolarization; RR=relative risk; SD=standard deviation; VD=ventricular depolarization; yrs=years.

Table 13. Exercise Capacity or Fitness Level on Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Measure of exercise capacity or fitness Prevalence	Effect Size of ECG abnormality compared to no abnormality (95% CI)
Aktas et al, 2004[95] *Study not named*	n=3,554 Mean age: 57 yrs (range, 50-75) 81% male Mean followup: 8 yrs	Impaired functional capacity (<9.5 METs for men, <7.5 for women): 25% Exercise capacity (number of METs): continuous variable	All-cause mortality Impaired functional capacity: HR, 3.0 (2.0-4.4) Exercise capacity (per 1 MET decrease): HR, 1.3 (1.2-1.4), adjusted for exercise ECG variables
Blair et al, 1996[97] *Aerobics Center Longitudinal Study* Other publications: Wei et al, 1999[151]	n=32,421 Mean age: 43 yrs (range, 20-88) 79% male Mean followup: 8.2 yrs	Low fitness level (based on treadmill time, least fit 20% of study population): 20%	CVD death Men: HR, 1.7 (1.3-2.2) Women: HR, 2.4 (0.99-5.9) All-cause mortality Men: HR, 1.5 (1.3-1.8) Women: HR, 2.1 (1.4-3.3)
Gulati et al, 2003[105] *St. James Women Take Heart*	n=5,271 Mean age: 52 yrs (range NR [SD, 11]) 0% male Mean followup: 8.4 yrs	Exercise capacity (<5, 5-8, or >8 METs): NR	All-cause mortality <5 METs vs. >8 METs: HR, 3.1 (2.1-4.8) 5-8 METs vs. >8 METs: HR, 1.9 (1.3-2.9)
Gulati et al, 2005[104] *St. James Women Take Heart* Same population as Gulati et al, 2003[105]	n=5,636 Mean age: 52 yrs (range NR [SD, 11]) 0% male Mean followup: 8.4 yrs	Exercise capacity (number of METs): continuous variable	CHD death (per unit MET increase): HR, 0.83 (0.78-0.89) All-cause mortality (per unit MET increase): HR, 0.83 (0.78-0.89)
Laukkanen et al, 2008[113] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,639 Mean age: 52 yrs (range, 42-60 yrs) 100% male Mean followup: 16.6 yrs	Exercise capacity, based on highest workload achieved during exercise test, categorized into quartiles (<162 W [lowest quartile] vs. >230 W [highest quartile]) and per 20 W increment	CVD death <162 W vs. >230 W: HR, 2.0 (1.1-3.6) Per 20 W increment: HR, 0.86 (0.79-0.93) Major CVD event <162 W vs. >230 W: HR, 1.9 (1.4-2.7) Per 20 W increment: HR, 0.88 (0.84-0.93) All-cause mortality <162 W vs. >230 W: HR, 2.5 (1.7-3.7) Per 20 W increment: HR, 0.85 (0.80-0.89)
Peters et al, 1983[121] *Study not named*	n=2,779 Median age: 41 yrs (range, 35-53) 100% male Mean followup: 4.8 yrs	Physical work capacity (maximum average power output during 5-min intervals of exercise testing) below median for age group	Fatal or nonfatal MI: RR, 2.2 (1.1-4.7)
Rywik et al, 2002[125] *Baltimore Longitudinal Study of Aging*	n=1,083 Mean age: 52 yrs (range NR [SD, 18]) 57% male Mean followup: 7.9 yrs	Duration of exercise (minutes): continuous variable	Coronary events (angina, nonfatal MI, CHD death) (per minute): HR, 0.87 (0.79-0.96)

Table 13. Exercise Capacity or Fitness Level on Exercise ECG as a Predictor of Cardiovascular Events

Author, year *Study*	Sample size Demographics Duration of followup	Measure of exercise capacity or fitness Prevalence	Effect Size of ECG abnormality compared to no abnormality (95% CI)
Savonen et al, 2007[126] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,314 Mean age: 52 yrs (range, 42-61) 100% male Mean followup: 11.5 yrs	Workload achieved at 100/bpm (WL_{100}): continuous variable	CHD death (per decrement of 31 W): HR, 1.9 (1.3-2.8) CVD death (per decrement of 31 W): HR, 1.7 (1.3-2.4) All-cause mortality (per decrement of 31 W): NS (data NR)
Sui et al, 2007[129] *Aerobics Center Longitudinal Study*	n=26,637 Mean age: NR (range, 18-83 yrs) 78% male Mean followup: 10 yrs	Fitness level, based on duration of maximal treadmill exercise test: low=lowest quintile; moderate=2nd and 3rd quintiles; high=upper 2 quintiles	CVD event (MI, revascularization, stroke) vs. low fitness level group *Men* Moderate fitness level: HR, 0.89 (0.78-1.0) High fitness level: HR, 0.75 (0.64-0.87) *Women* Moderate fitness level: HR, 0.83 (0.54-1.3) High fitness level: HR, 0.78 (0.49-1.2)

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; METs=metabolic equivalents; MI=myocardial Infarction; NR=not reported; NS=not significant; RR=relative risk; SD=standard deviation; yrs=years.

Table 14. Other Findings on Exercise ECG as Predictors of Cardiovascular Events

Author, year	Sample Size Demographics Duration of followup	Exercise ECG abnormality Prevalence	Effect size of ECG abnormality compared to no abnormality (95% CI)
Blair et al, 1996[97] *Aerobics Center Longitudinal Study* Other publications: Wei et al, 1999[151]	n=32,421 Mean age: 43 yrs (range, 20-88) 79% male Mean followup: 8.2 yrs	Nonspecific ECG changes at rest or with exercise: 6.8%	CVD death Men: HR, 3.0 (2.2-4.0) Women: HR, 5.0 (1.9-13) All-cause mortality Men: HR, 1.6 (1.3-2.0) Women: HR, 1.6 (0.87-2.8)
Gulati et al, 2005[104] *St. James Women Take Heart* Same population as Gulati et al, 2003[105]	n=5,636 Mean age: 52 yrs (range NR [SD, 11]) Mean followup: 9 yrs	Duke treadmill score (exercise time - [5 x ST deviation] - [4 x angina score index]) <5: NR (mean score, 8)	CHD death: HR, 2.7 (1.6-4.8) All-cause mortality: HR, 2.2 (1.6-3.1)
Laukkanen et al, 2006[112] *Kuopio Ischemic Heart Disease Risk Factor Study*	n=1,596 Mean age: 52 yrs (range, 42-61) 100% male Mean followup: 14 yrs	Peak oxygen pulse (VO_2 max/ maximum heart beat): continuous variable	CHD death (reference: peak oxygen pulse >17.8 ml/beat) Peak oxygen pulse <13.5: HR, 2.4 (1.1-5.4) Peak oxygen pulse 13.5-15.7: HR, 1.2 (0.52-2.8) Peak oxygen pulse 15.8-17.8: HR, 1.3 (0.59-3.0) All-cause mortality (reference: peak oxygen pulse >17.8 ml/beat) Peak oxygen pulse <13.5: HR, 1.8 (1.2-2.6) Peak oxygen pulse 13.5-15.7: HR, 1.2 (0.80-1.8) Peak oxygen pulse 15.8-17.8: HR, 1.2 (0.81-1.8)
Mora et al, 2005[117] *Lipid Research Clinics Prevalence Study*	n=6,126 Mean age: 45 yrs (range NR [SD, 10]) 54% male 96% white (other races NR) Followup: 10 yrs and 20 yrs	Heart rate recovery (based on peak exercise heart rate - heart rate 2 min after exercise) and exercise capacity (METs), categorized into high or low groups based on sex-specific medians High heart rate recovery and high METs: 28% Low heart rate recovery or low METs: 41% Low heart rate recovery and low METs: 31%	CVD death *10-yr followup* High heart rate recovery and high METs: HR, 1 (referent) Low heart rate recovery or low METs: HR, 1.1 (0.40-2.9) in men; HR, 1.4 (0.36-5.3) in women Low heart rate recovery and low METs: HR, 2.7 (1.1-6.6) in men; HR, 3.8 (1.1-13) in women *20-yr followup* High heart rate recovery and high METs: HR, 1 (referent) Low heart rate recovery or low METs: HR, 1.5 (0.83-2.7) in men; HR, 3.1 (1.3-7.4) in women Low heart rate recovery and low METs: HR, 3.5 (2.0-6.2) in men; HR, 8.5 (3.6-20) in women
Okin et al, 1991[119] *Framingham Offspring Study*	n=3,168 Mean age: 44 yrs (range, 17-70 [SD, 10]) 48% male Race NR Mean followup: 4.3 yrs	Heart rate adjusted ST segment depression index ≥1.6 μV bpm: 8.7% Abnormal rate-recovery loop: 6.0%	Abnormal heart rate adjusted ST segment depression index + abnormal rate-recovery loop (vs. both normal): HR, 2.7 (1.8-4.0) Abnormal heart rate adjusted ST segment depression index + normal rate-recovery loop, or normal heart rate adjusted ST segment depression index + abnormal rate-recovery loop (vs. both normal): HR, 1.6 (1.1-2.5)

Abbreviations: bpm=beats per minute; CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; METs=metabolic equivalents;NR=not reported; SD=standard deviation; yrs=years.

Table 15. Estimates of Risk Associated With Exercise ECG Abnormalities, Stratified By Sex

Author, year *Study*	Sample Size Demographics Duration of followup	Definition of abnormality Prevalence	Risk associated with abnormality compared to no abnormality in men (95% CI)	Risk associated with abnormality compared to no abnormality in women (95% CI)
Balady et al, 2004[96] *Framingham Heart Study*	n=3,043 Mean age: 45 yrs (range, 30-70) 47% male Mean followup: 18 yrs	≥1 mm horizontal or downsloping ST segment depression in 3 consecutive beats: 4.3%	Any CHD event: HR, 1.8 (1.2-2.9)	Any CHD event: HR, 1.9 (0.91-4.0)
Balady et al, 2004[96] *Framingham Heart Study* Other publications: Framingham Study[150]	n=3,043 Mean age: 45 yrs (range, 30-70) 47% male Mean followup: 18 yrs	Failure to reach 85% of predicted maximum heart rate: 9.0%	Any CHD event: HR, 1.8 (1.2-2.4)	Any CHD event: HR, 1.3 (0.74-2.4)
Blair et al, 1996[97] *Aerobics Center Longitudinal Study*	n=32,421 Mean age: 43 yrs (range, 20-88) 79% male Mean followup: 8.2 yrs	Abnormal ECG (not defined): 6.8%	CVD death: HR, 3.0 (2.2-4.0) All-cause mortality: HR, 1.6 (1.3-2.0)	CVD death: HR, 5.0 (1.9-13) All-cause mortality: HR, 1.6 (0.87-2.8)
Blair et al, 1996[97] *Aerobics Center Longitudinal Study*	n=32,421 Mean age: 43 yrs (range, 20-88) 79% male Mean followup: 8.2 yrs	Low fitness level (based on treadmill time, least fit 20% of study population): 20%	CVD death: HR, 1.7 (1.3-2.2) All-cause mortality: HR, 1.5 (1.3-1.8)	CVD death: HR, 2.4 (0.99-5.9) All-cause mortality: HR, 2.1 (1.4-3.3)
Sui et al, 2007[129] *Aerobics Center Longitudinal Study*	n=26,637 Mean age: NR (range, 18-83) 78% male Mean followup: 10 yrs	Fitness level, based on duration of maximal treadmill exercise test: low=lowest quintile; moderate=2nd and 3rd quintiles; high=upper 2 quintiles	CHD event (revascularization or MI) Low fitness level: HR, 1 (referent) Moderate fitness level: HR, 0.87 (0.77-1.0) High fitness level: HR, 0.76 (0.63-0.89)	CHD event (revascularization or MI) Low fitness level: HR, 1 (referent) Moderate fitness level: HR, 0.93 (0.54-1.6) High fitness level: HR, 0.82 (0.45-1.5)
Mora et al, 2005[117] *Lipid Research Clinics Prevalence Study*	n=6,126 Mean age: 45 yrs (range NR [SD, 10]) 54% male Mean followup: 20 yrs	Abnormal heart rate recovery (peak exercise heart rate − heart rate 2 min after exercise) and low exercise capacity (based on METs); categorized into high or low groups based on sex-specific medians High heart rate recovery and high METs: 28% Low heart rate recovery or low METs: 41% Low heart rate recovery and low METs: 31%	CVD death High heart rate recovery and high exercise capacity: HR, 1 (referent) Low heart rate recovery or low exercise capacity: HR, 1.5 (0.83-2.7) Low heart rate recovery and low exercise capacity: HR, 3.5 (2.0-6.2)	CVD death High heart rate recovery and high exercise capacity: HR, 1 (referent) Low heart rate recovery or low exercise capacity: HR, 3.1 (1.3-7.4) Low heart rate recovery and low exercise capacity: HR, 8.5 (3.6-20)

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; METs=metabolic equivalents; MI=myocardial infarction; NR=not reported; SD=standard deviation; yrs=years.

Table 16. Abnormalities on Exercise ECG as Predictors of Cardiovascular Events in Persons With Diabetes

Author, year *Study*	Sample size Demographics Duration of followup	Exercise ECG abnormality Prevalence	Risk associated with ECG abnormality compared to no abnormality (95% CI)
Lyerly et al, 2008[114] *Aerobics Center Longitudinal Study*	n=2,854 Mean age: 50 yrs (range, 21-84) 100% male All with diabetes Mean followup: 16 yrs	ST segment depression or elevation ≥1 mm ≥0.08 s from the J-point: 11% ST segment depression 0.5-1.0 mm ≥0.08 s: 11%	CHD death ST depression or elevation ≥1 mm: HR, 2.1 (1.3-3.3) ST segment depression 0.5-1.0 mm: HR, 1.7 (1.0-2.8) CVD death ST segment depression or elevation ≥1 mm: HR, 2.0 (1.4-2.8) ST segment depression 0.5-1.0 mm: HR, 1.6 (1.1-2.5) All-cause mortality ST segment depression or elevation ≥1 mm: HR, 1.4 (1.1-1.8) ST segment depression 0.5-1.0 mm: HR, 1.4 (1.1-1.9)
Lyerly et al, 2009[115] *Aerobics Center Longitudinal Study*	n=3,044 Mean age: 47 yrs (range, 20-79) 100% female All with impaired glucose tolerance or undiagnosed diabetes Mean followup: 16 yrs	Fitness level, based on age-specific maximal exercise duration and oxygen uptake in METs Low fitness level: 17% Moderate fitness level: 34% High fitness level: 49%	All-cause mortality Low fitness level: HR, 1 (referent) Moderate fitness level: HR, 0.65 (0.45-0.94) High fitness level: HR, 0.64 (0.43-0.95)
Rutter et al, 2002[123] *Study not named* Other publication: Rutter et al, 1999[153]	n=86 Mean age: 62 yrs (range, 45-75) 72% male All with diabetes Mean followup: 2.8 yrs	ST segment depression (>1 mm horizontal or downsloping ST-segment depression at 80 ms after J-point for 3 consecutive beats): 52%	Any CHD event (cardiac death, MI, or new-onset angina): HR, 21 (2-204)

Abbreviations: CHD=coronary heart disease; CI=confidence interval; CVD=cardiovascular disease; ECG=electrocardiography; HR=hazard ratio; METs=metabolic equivalents; MI=myocardial infarction; yrs=years.

Table 17. Prospective Cohort Studies Describing Downstream Results of Exercise Treadmill Test Screening in Asymptomatic Populations

Author, year	Population	Sample size Demographics	ETT abnormality and proportion with abnormality	Subsequent testing	CHD diagnosis following testing	Subsequent treatment following testing
Aktas et al, 2004[95]	Asymptomatic members of a preventive executive health program	n=3,554 Mean age: 57 yrs (range, 50-75) 81% male 2% black (other races NR)	Ischemic ST changes 1 mm horizontal or down-sloping depression occurring 80 ms after the J-point in at least 3 consecutive beats and 2 contiguous leads: 10.4% (371/3554)	Nuclear or echocardiography stress imaging: 5.3% (190/3554) Angiography: 0.6% (21/3554)	Nuclear or echo-cardiography stress imaging: 0.5% (16/ 3554) had evidence of ischemia or scar Angiography: 0.06% (2/3554) stenosis	Angiography: 0.08% (3/3554) CABG: 0.03% (1/3554) revascularization
Blumenthal et al, 2003[134]	Siblings with family history of CHD and no known CAD	n=734 Mean age: 49 yrs* 79% male 24% black (other races NR) **Age reported only for subset of patients with abnormal ETT and/or scintigram*	Abnormal ETT and/or scintigram Presence of reversible ischemia: 20.8%	Angiography: 1.43% (105/743)	≥1 coronary artery with ≥50% stenosis: 5.5% (41/743) ≥1 coronary artery with ≥70% stenosis: 3.2% (24/743)	NR
Boyle et al, 1987[135]	Random, asymptomatic UK factory workers	n=1,194* Mean age: NR (range, 19-64 yrs) 95% male Race NR **20 participants excluded from analysis; 10 due to incomplete testing, 5 due to inadequate ECG data, 5 due to development of CHD symptoms*	ST segment/heart rate slope >13 mm beats^{-1}/min/10^{-3} twice within 1 month: 5.8% (68/1174)	Angiography: 2% (24/1174) Further assessment (undefined): 3.3% (39/1174)	Significant coronary narrowing: 0.77% (9/1174)	NR
Cournot et al, 2006[99]	Asymptomatic, consecutively enrolled, self- and physician-referred from general population	n=1,051 Mean age: 52 yrs (range, 18-79) 64% male Race NR	Positive ETT ST segment depression ≥1.0 mm at 80 ms after the J-point in at least 2 leads: 8.5% (89/1051)	Angiography: 1.7% (18/1051)	NR	Revascularization: 0.48% (5/1051)
Davies et al, 1996[136]	Asymptomatic, self- and physician-referred from general population	n=5,000 Mean age: 54 yrs (range, 30-65)* 100% male Race NR **Age reported only for subset of patients with positive stress test*	Positive ECG Any of the following conditions: fatigue during test, dyspnea, angina, ST segment depression or elevation of ≥1 mm, significant arrythmia: 3.2% (162/5000)	Angiography: 1.7% (86/5000)	CAD (≥75% diameter narrowing of at least one major coronary artery): 1.3% (67/5000)	CABG: 0.5% (26/5000) Angioplasty: 0.1% (7/5000) Medical treatment: 0.7% (34/5000)

Table 17. Prospective Cohort Studies Describing Downstream Results of Exercise Treadmill Test Screening in Asymptomatic Populations

Author, year	Population	Sample size Demographics	ETT abnormality and proportion with abnormality	Subsequent testing	CHD diagnosis following testing	Subsequent treatment following testing
Dunn et al, 1991[137]	Employee- and self-referred patients at a preventive medicine clinic; known CAD excluded	n=1,930 Mean age: NR (range, 22-85 yrs) Median age: 48 yrs in normal ETT group vs. 59 yrs in abnormal ETT group 85% male Race NR	Abnormal ETT ≥1 mm horizontal or downsloping ST segment depression 80 ms after the J-point: 8.5% (155/1930) (8.4% [137/1633] in men; 6% [18/297] in women)	Angiography: 1.2% (23/1930) (1.3% [22/1633] in men; 0.3% [1/297] in women) Thallium scan: 4% (77/1930) (4.3% [71/1633] in men; 2% [6/297] in women)	CAD (abnormal ETT + abnormal thallium scan or abnormal angiography): 1.3% (25/1930) (1.5% [24/1633] in men; 0.3% [1/297] in women)	CABG: 0.3% (6/1930) Percutaneous transluminal coronary angioplasty: 0.6% (11/1930) Medical treatment: 0.4% (8/1930)
Hollenberg et al, 1985[132]	Asymptomatic, military officers	n=377 Mean age: 37 yrs (range, 31-48) 100% male Race NR	Abnormal ETT ≥1 mm horizontal or down-sloping ST segment depress-ion 80 ms after the J-point (defined as con-ventional assessment): 12% (45/377)	Angiography: 2.7% (10/377)	Mild CAD (60% proximal obstruction and 70% distal obstruction of right coronary artery): 0.3% (1/377)	NR
Livschitz et al, 2000[138]	Healthy, male soldiers age >39 yrs undergoing routine physical exam	n=4,900 Mean age: 43 yrs (range NR) 100% male Race NR	Abnormal ETT Exercise-induced chest pain and hypotension, horizontal or downsloping ST depress-ion ≥1 mm, or 1.5 mm upsloping depression 80 ms after the J-point: 6.1% (299/ 4900)	Angiography: 0.8% (4/4900) Repeat study: 2.2% (106/4900) Thallium scan: 2% (78/4900)	CAD: 0.06% (3/4900)	CABG: 0.02% (1/4900) Percutaneous transluminal coronary angioplasty: 0.02% (1/4900)
Massie et al, 1993[139]	Asymptomatic veterans with hypertension recruited at VA hypertension clinic	n=201 (completed ETT) Mean age: 61 yrs (range NR) 100% male 80% white or Asian (other races NR)	Positive ETT ≥1 μV horizontal or down-sloping ST-segment depression 80 ms after the J-point: 33% (67/201) (includes 180 definitive tests and 21 inconclusive tests)	Angiography: 12.9% (26/201)	CAD: 7% (14/201)	NR
Piepgrass et al, 1982[140]	Asymptomatic, male Air Force personnel undergoing routine physical exam	n=771 Mean age: 42 yrs (range, 35-54) 100% male Race NR	Abnormal ETT ≥1 μV ST depression 80 ms from the J-point: 3.5% (27/771)	Angiography: 2.5% (19/771)	CAD: 0.5% (4/771)	Removal from duty: 1.1% (8/771) (4 due to CAD, 4 due to declining angiography)

Table 17. Prospective Cohort Studies Describing Downstream Results of Exercise Treadmill Test Screening in Asymptomatic Populations

Author, year	Population	Sample size Demographics	ETT abnormality and proportion with abnormality	Subsequent testing	CHD diagnosis following testing	Subsequent treatment following testing
Pilote et al, 1998[141]	Asymptomatic, consecutively enrolled adults undergoing routine physical exam	n=4,334 Mean age: 52 yrs (median, 51; range NR) 83% male Race NR	Abnormal ETT Presence of ischemic ST-segment changes, drop in blood pressure of ≥10 mmHg, anginal chest pain, failure to reach 85% of maximum age-predicted target heart rate: 14.6% (633/4334)	Angiography: 2.9% (126/4334) Thallium scan: 2.4% (105/4334)	CAD: 1.6% (71/4334) (includes 19 cases [0.4%] of severe CAD)	CABG: 0.8% (34/4334) Percutaneous transluminal coronary angioplasty: 0.4% (16/4334)

Abbreviations: CABG=coronary artery bypass graft; CAD=coronary artery disease; CHD=coronary heart disease; ECG=electrocardiography; ETT=exercise treadmill test; NR=not reported; UK=United Kingdom; VA=U.S. Department of Veterans Affairs; yrs=years.

Table 18. Summary of Evidence

Number of studies	Limitations	Consistency	Primary care applicability	Summary of findings
KQ 1. What are the benefits of screening for abnormalities on resting or exercise ECG compared to no screening on CHD outcomes?				
No studies	No studies met inclusion criteria	No evidence	No evidence	No randomized controlled trials or controlled observational studies on screening asymptomatic adults for CHD with resting or exercise ECG versus no screening were identified.
KQ 2. How does the identification of high-risk persons via resting or exercise ECG affect use of treatments to reduce cardiovascular risk?				
No studies	No studies met inclusion criteria	No evidence	No evidence	No studies that evaluated how screening individuals for CHD using resting or exercise ECGs affects use of interventions to reduce cardiovascular risk were identified.
KQ 3. What is the accuracy of resting or exercise ECG for stratifying persons into high-, intermediate-, and low-risk groups?				
63 studies *Overall quality rating: fair*	No study estimated how adding ECG results to traditional risk factors affected discrimination or calibration, or provided data to enable the construction of risk stratification tables	Consistent	High	No study estimated how accurately resting or exercise ECG plus traditional risk factor assessment classified subjects into high-, intermediate-, or low-risk groups compared to classification based on traditional risk factor assessment alone, or provided data to enable the construction of risk stratification tables in order to estimate risk reclassification rates. Two studies found that resting or exercise ECG findings plus traditional risk factor assessment resulted in a slight increase in the C statistic compared to traditional risk factor assessment alone, but differences were not statistically significant in one study, and the level of statistical significance was not reported in the other. Pooled analyses showed that abnormalities on resting (ST segment or T wave abnormalities, LVH, bundle branch block, left axis deviation) or exercise (ST segment depression with exercise, failure to reach maximum target heart rate) ECG were associated with an increased risk (HR estimates from 1.4 to 2.1) of subsequent cardiovascular events, after adjusting for traditional risk factors. Statistical heterogeneity was present in a number of analyses, but stratification of studies by method of defining the ECG abnormality, study quality, or the type of cardiovascular events evaluated did not reduce heterogeneity and resulted in similar estimates. Low versus high exercise capacity or fitness during exercise ECG was also associated with increased risk of subsequent cardiovascular events or all-cause mortality (HR estimates from 1.7 to 3.1), but results from individual studies could not be pooled.
KQ 4. What are the harms of screening with resting or exercise ECG?				
2 studies *Overall quality rating: poor*	Only two uncontrolled studies examined harms associated with screening ECG	Consistent	Low (limited evidence)	No studies reported harms directly associated with screening with resting ECG. One study (included in the previous report) found no complications in 377 subjects who underwent screening with exercise ECG. No studies reported downstream harms associated with followup testing or interventions after screening with resting or exercise ECG.

Abbreviations: CHD=coronary heart disease; ECG=electrocardiography; HR=hazard ratio; KQ=key question; LVH=left ventricular hypertrophy.

Appendix A. Abbreviations and Acronyms

Abbreviation/Acronym	Definition
AAFP	American Academy of Family Physicians
ABI	Ankle-brachial index
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACP	American College of Physicians
ACPM	American College of Preventive Medicine
ACSM	American College of Sports Medicine
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ARIC	Atherosclerosis Risk in Community
AVR	Aortic valve replacement
BIRNH	Belgian Inter-University Research on Nutrition and Health
BP	Blood pressure
bpm	Beats per minute
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAS	Coronary artery stenosis
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CT	Computed tomography
CVA	Cerebral vascular accident
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EBCT	Electron-beam computed tomography
ECG	Electrocardiography
ETT	Exercise treadmill test
HDL	High-density lipoprotein
HR	Hazard ratio
HRV	Heart rate variability
KQ	Key question
LDL	Low-density lipoprotein
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MET	Metabolic equivalent
MI	Myocardial infarction
MN	Minnesota
MRFIT	Multiple Risk Factor Intervention Trial
NHANES	National Health and Nutrition Examination Survey
NR	Not reported
NS	Not significant
OR	Odds ratio
PCI	Percutaneous coronary intervention
PVD	Premature ventricular depolarization
RCT	Randomized controlled trial

Appendix A. Abbreviations and Acronyms

RIFLE	Risk Factors and Life Expectancy
RR	Relative risk
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
SD	Standard deviation
USPSTF	U.S. Preventive Services Task Force
VA	U.S. Department of Veteran Affairs
VD	Ventricular depolarization
VPC	Ventricular premature complex
WHI	Women's Health Initiative
WOSCOPS	West of Scotland Coronary Prevention Study

Database: Ovid MEDLINE

Key Question 1: Screening

1 Electrocardiography, ambulatory/ or electrocardiography/ or electrocardiography.mp.
2 (ekg or ecg).mp.
3 1 or 2
4 Exercise test/
5 (treadmill adj2 test).mp.
6 (treadmill and ett).mp.
7 or/4-6
8 3 or 7
9 Myocardial ischemia/
10 8 and 9
11 Mass screening/
12 10 and 11
13 limit 12 to yr="2002-2009"
14 limit 13 to humans
15 from 14 keep 1-11

Key Questions 2 & 3: Risk stratification and diagnostic accuracy

1 Electrocardiography, ambulatory/ or electrocardiography/ or electrocardiography.mp.
2 (ekg or ecg).mp.
3 1 or 2
4 Exercise test/
5 (treadmill adj2 test).mp.
6 (treadmill and ett).mp.
7 or/4-6
8 3 or 7
9 Myocardial ischemia/th, mo, di, ep, pc
10 (coronary heart disease or chd).mp.
11 9 or 10
12 8 and 11
13 exp risk/
14 12 and 13
15 limit 14 to yr="2002-2009"
16 limit 15 to humans
17 limit 15 to English language
18 16 and 17
19 limit 18 to "all adult (19 plus years)"
20 from 19 keep 1-406

Key Question 4: Harms

1 Electrocardiography, ambulatory/ or electrocardiography/ or electrocardiography.mp.
2 (ekg or ecg).mp.
3 1 or 2
4 Exercise test/

5 (treadmill adj2 test).mp.
6 (treadmill and ett).mp.
7 or/4-6
8 3 or 7
9 (medical errors or iatrogenic disease or false positive reactions).sh.
10 8 and 9
11 limit 10 to (English language and humans)
12 11 and (comparative study or clinical trial or controlled clinical trial or randomized controlled trial).pt.
13 from 12 keep 1-134

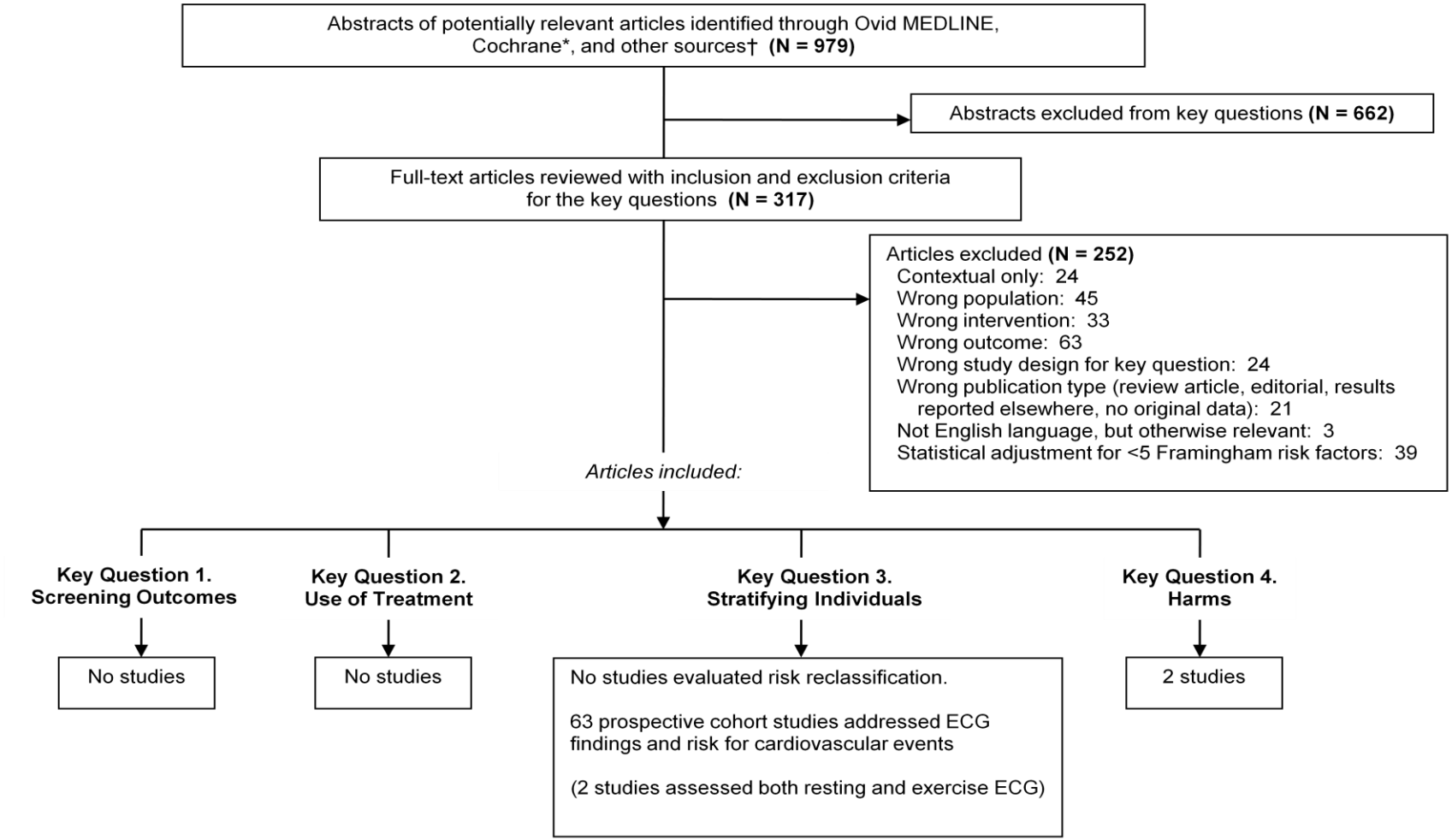
Database: Cochrane Central Register of Controlled Trials

1 Electrocardiography, ambulatory/ or electrocardiography/ or electrocardiography.mp.
2 (ekg or ecg).mp.
3 1 or 2
4 Exercise test/
5 (treadmill adj2 test).mp.
6 (treadmill and ett).mp.
7 or/4-6
8 3 or 7
9 Myocardial ischemia/th, mo, di, ep, pc
10 (coronary heart disease or chd).mp.
11 9 or 10
12 8 and 11
13 exp risk/
14 12 and 13
15 limit 14 to yr="2002-2009"

Appendix B2. Inclusion and Exclusion Criteria

	Inclusion criteria	Exclusion criteria
Settings	Studies performed in settings generalizable to primary care Studies performed in United States, Canada, and Europe	Studies performed in specialty settings Studies of patients undergoing preoperative evaluation
Populations	Adults ages >18 years without symptoms of coronary heart disease (accepted studies with mixed populations of asymptomatic and symptomatic persons if results were reported separately for asymptomatic persons or <10% of the sample was symptomatic)	Persons with a history of atherosclerotic disease or symptoms suggesting coronary heart disease
Interventions	Resting electrocardiography Exercise electrocardiography	Radiological tests (e.g., thallium scans, scintigraphy, and computed tomography) Echocardiography Vectorcardiography
Outcomes	Coronary heart disease death Cardiovascular disease death Myocardial infarction Angina Stroke Congestive heart failure Composite cardiovascular outcomes All-cause mortality Anxiety, labeling Complications of procedures or treatments initiated as a result of screening	Radiographic progression of coronary artery disease
Study types		
Benefits (KQ 1) and use of interventions to reduce cardiovascular risk (KQ 2)	Randomized controlled trials involving resting or exercise electrocardiography in asymptomatic people Controlled observational studies	Non-systematic reviews Case-control studies Cross-sectional studies Hybrid designs that do not clearly stipulate followup and ascertainment procedures Case reports and other uncontrolled studies
Diagnostic accuracy and risk prediction (KQ 3)	Prospective cohort studies that controlled for at least 5 of 7 Framingham cardiovascular risk factors and reported rates of subsequent cardiovascular events	
Harms (KQ 4)	Randomized controlled trials involving resting or exercise electrocardiography in asymptomatic people Controlled observational studies Large uncontrolled studies	Case reports Cross-sectional studies

Appendix B3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, suggested by experts.

Abbreviations: ECG=electrocardiography.

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Resting ECG studies		
Bodegard et al, 2004[66]	None	Government employees in Oslo, Norway
Brown, Giles, and Croft, 2000[67]	None	National Health and Nutrition Examination Survey II
Crow, Hannah, and Folsom, 2003[68]	None	Atherosclerosis Risk in Community Study
Cuddy and Tate, 2006[69]	Mathewson FA, Varnam GS. Abnormal electrocardiograms in apparently healthy people, II: the electrocardiogram in the diagnosis of subclinical myocardial disease—serial records of 32 people. *Circulation.* 1960;21:204-13. Tate RB, Lah L, Cuddy TE, et al. Definition of successful aging by elderly Canadian males: the Manitoba Follow-up Study. *Gerontologist.* 2003;43(5):735-44.	Manitoba Follow-Up Study
Daviglus et al, 1999[70]	Paul O, Lepper MH, Phelan WH, et al. A longitudinal study of coronary heart disease. *Circulation.* 1963;28:20-31.	Chicago Western Electric Study
De Bacquer et al, 1998[71]	Regional differences in dietary habits, coronary risk factors and mortality rates in Belgium, 1: design and methodology. *Acta Cardiol*. 1984;39(4):285-92. Kornitzer M, Dramaix M. The Belgian Inter-university Research on Nutrition and Health (BIRNH.) study. *Acta Cardiol*. 1989;94:89-99.	Belgian Inter-University Research on Nutrition and Health Study
Denes et al, 2007[72]	Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2003;349(6):523-34.	Women's Health Initiative
Dhingra et al, 2006[73]	None	Framingham Heart Study
Diercks et al, 2002[74]	Hillege HL, Janssen WM, Bak AA, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med*. 2001;249(6):519-26. Diercks GF, van Boven AJ, Hillege HL, et al. Microalbuminuria is independently associated with ischaemic electrocardiographic abnormalities in a large non-diabetic population: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. *Eur Heart J.* 2000;21(23):1922-7.	Prevention of Renal and Vascular End-stage Disease Study
Gottdiener et al, 2000[75]	Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. *Am J Med.* 2003;115(9):689-94.	Cardiovascular Health Study
Greenland et al, 2003[76]	Stamler J, Rhomberg P, Schoenberger JA, et al. Multivariate analysis of the relationship of seven variables to blood pressure: findings of the Chicago Heart Association Detection Project in Industry, 1967-1972. *J Chronic Dis.* 1975;28(10):527-48.	Chicago Heart Association Detection Project in Industry
Kahn et al, 1996[79]	Nadelmann J, Frishman W, Ooi W. Prevalence, incidence and prognosis of recognized and unrecognized myocardial infarction in persons aged 75 years or older: the Bronx Aging Study. *Am J Cardiol.* 1990;66(5):533-7.	Bronx Aging Study

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Larsen et al, 2002[80]	None	Copenhagen City Heart Study
Liao et al, 1988[81]	Stamler J, Rhomberg P, Schoenberger JA, et al. Multivariate analysis of the relationship of seven variables to blood pressure: findings of the Chicago Heart Association Detection Project in Industry, 1967-1972. *J Chronic Dis.* 1975;28(10):527-48.	Chicago Heart Association Detection Project in Industry
Macfarlane et al, 2007[77]	Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333(20):1301-7. WOSCOPS Study Group. A coronary primary prevention study of Scottish men aged 45-64 years: trial design. *J Clin Epidemiol.* 1992;45(8):849-60.	West of Scotland Coronary Prevention Study
Machado et al, 2006[82]	Vitelli LL, Crow RS, Shahar E, et al. Electrocardiographic findings in a healthy biracial population. *Am J Cardiol.* 1998;81:453-9.	Atherosclerosis Risk in Community Study
Massing et al, 2006[83]	The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol.* 1989;129(4):687-702.	Atherosclerosis Risk in Community Study
Menotti et al, 1997[84]	Presentation of the RIFLE project risk factors and life expectancy. *Eur J Epidemiol.* 1993;9(5):459-76. Menotti A, Keys A, Kromhout D, et al. Inter-cohort differences in coronary heart disease mortality in the 25-year follow-up of the seven countries study. *Eur J Epidemiol.* 1993;9(5):527-36.	Risk Factors and Life Expectancy Project
Menotti et al, 2001[85]	None	FINE (Finland, Italy, and the Netherlands) Study
Moller et al, 2007[86]	Hedstrand H. A study of middle-aged men with particular reference to risk factors for cardiovascular disease. *Ups J Med Sci Suppl.* 1975;19:1-61.	Uppsala Longitudinal Study of Adult Men
Prineas et al, 2002[88]	Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA*. 1982;248(12):1465-77.	Multiple Risk Factor Intervention Trial
Rautaharju et al, 2006[89]	Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials.* 1998;19(1):61-109. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-33. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med.* 2003;349(6):523-34.	Women's Health Initiative
Rautaharju et al, 2006[90]	Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol.* 1995;5(4):278-85. Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol.* 1998;31(3):157-87.	Cardiovascular Health Study

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Sigurdsson et al, 1996[92]	Sigurdsson E, Sigfusson N, Agnarsson U, et al. Long-term prognonsis of different forms of coronary heart disease: the Reykjavik study. *Int J Epidemiol.* 1995;24(1):58-68. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Prevalence of coronary heart disease in Icelandic men 1968-1986. *Eur Heart J.* 1993;14:584-91. Sigurdsson E, Thorgeirsson G, Sigvaldason H, Sigfusson N. Unrecognized myocardial infarction: epidemiology, clinical characteristics, and the prognostic role of angina pectoris. *Ann Intern Med.* 1995;122(2):96-102.	Reykjavik Study
Sutherland et al, 1993[93]	Boyle E, Griffey WP, Nichaman MZ, Talbert CR. An epidemiologic study of hypertension among racial groups of Charleston County, SC: the Charleston Heart Study, phase II. In: *The Epidemiology of Hypertension*. New York: Grune & Stratton; 1967:193-203.	Charleston Heart Study
Exercise treadmill test studies		
Adabag et al, 2008[94]	Coronary heart disease death, nonfatal acute myocardial infarction and other clinical outcomes in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1986;58(1):1-13.	Multiple Risk Factor Intervention Trial
Aktas et al, 2004[95]	None	Unamed Clevland Clinic study
Balady et al, 2004[96]	Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol.* 1979;110(3):281-90.	Framingham Heart Study
Blair et al, 1996[97]	None	Aerobics Center Longitudinal Study
Bodegard et al, 2004[66]	None	Government employees in Oslo, Norway
Cole et al, 2000[98]	Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1979;60(2):427-39. Williams OD, Mowery RL, Waldman GT. Common methods, different populations: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1980;62(4 Pt 2):iv18-23. Criqui MH, Haskell WL, Heiss G, et al. Predictors of systolic blood pressure response to treadmill exercise: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1983;68(2):225-33. Ekelund LG, Haskell WL, Johnson JL, et al. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men: the Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med.* 1988;319(21):1379-84.	Lipid Research Clinics Program Prevalence Study
Cournot et al, 2006[99]	None	French general population (self- or physician-referred)

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Ekelund et al, 1989[100]	The Coronary Primary Prevention Trial: design and implementation. *J Chronic Dis.* 1979;32(9-10):609-31. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease. *JAMA.* 1984;251(3):351-64. Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise tolerance test for mortality in North American men: the Lipid Research Clinics Mortality Follow-up Study. *Circulation.* 1986;74(2):252-61.	Lipid Research Clinics Program Prevalence Study
Fleg et al, 1990[101]	Shock NW, Greulich RC, Andres RA, et al. Normal Human Aging: The Baltimore Study of Aging. Bethesda, MD: National Institutes of Health; 1984.	Baltimore Longitudinal Study on Aging
Giagnoni et al, 1983[102]	None	Unamed Lombard, Italy study
Gordon et al, 1986[103]	Plasma lipid distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1979;60(2):427-39. Heiss G, Tamir I, Davis CE, et al. Lipoprotein-cholesterol distributions in selected North American populations: the Lipid Research Clinics Program Prevalence Study. *Circulation.* 1980;61(2):302-15.	Lipid Research Clinics Program Prevalence Study
Gulati et al, 2003[105]	None	St. James Women Take Heart Project
Gulati et al, 2005[104]	None	St. James Women Take Heart Project
Josephson et al, 1990[106]	Shock NW, Greulich RC, Andres RA, et al. Normal Human Aging: The Baltimore Study of Aging. Bethesda, MD: National Institutes of Health; 1984.	Baltimore Longitudinal Study of Aging
Jouven and Ducimetiere, 2000[107]	Filipovsky J, Ducimetiere P, Safar M. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. *Hypertension.* 1992;20(3):333-9.	Paris Prospective Study
Kurl et al, 2003[108]	None	Kuopio Ischemic Heart Disease Risk Factor Study
Kurl et al, 2009[109]	None	Kuopio Ischemic Heart Disease Risk Factor Study
Lauer et al, 1996[110]	Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health.* 1951;41(3):279-81. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci.* 1963;107:539-56. Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families: the Framingham Offspring Study. *Am J Epidemiol.* 1979;110(3):281-90.	Framingham Heart Study
Laukkanen et al, 2001[111]	Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. *Ann Clin Res.* 1988;20(1-2):46-50.	Kuopio Ischemic Heart Disease Risk Factor Study
Laukkanen et al, 2006[112]	None	Kuopio Ischemic Heart Disease Risk Factor Study

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Lyerly et al, 2008[114]	None	Aerobic Center Longitudinal Study
Morshedi-Meibodi et al, 2002[118]	Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families. the Framingham Offspring Study. *Am J Epidemiol.* 1979;110(3):281-90.	Framingham Heart Study
Okin et al, 1991[119]	Feinleib M, Kannel WB, Garrison RJ, et al. The Framingham Offspring Study: design and preliminary data. *Prev Med.* 1975;4(4):518-25.	Framingham Heart Study
Okin et al, 1996[120]	Rautaharju PM, Prineas RJ, Eifler WJ, et al. Prognostic value of exercise electrocardiogram in men at high risk of future coronary heart disease: Multiple Risk Factor Intervention Trial experience. J *Am Coll Cardiol.* 1986;8(1):1-10. Statistical design considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). *J Chronic Dis.* 1977;30(5):261-75. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA.* 1982;248(12):1465-77. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1985;55(1):1-15. Multiple Risk Factor Intervention Trial Research Group. Exercise electrocardiogram and coronary heart disease mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1985;55:16-24.	Multiple Risk Factor Intervention Trial
Rautaharju et al, 1986[122]	Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA.* 1982;248(12):1465-77. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1985;55(1):1-15. Exercise electrocardiogram and coronary heart disease mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1985;55:16-24.	Multiple Risk Factor Intervention Trial
Rutter et al, 2002[123]	Rutter MK, McComb JM, Brady S, Marshall SM. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *Am J Cardiol.* 1999;83(1):27-31.	Clinic patients in England
Rywik et al, 1998[124]	Shock NW, Greulich RC, Andres RA, et al. Normal Human Aging: The Baltimore Study of Aging. Bethesda, MD: National Institutes of Health; 1984.	Baltimore Longitudinal Study of Aging
Savonen et al, 2007[126]	None	Kuopio Ischemic Heart Disease Risk Factor Study
Siscovick et al, 1991[127]	The Coronary Primary Prevention Trial: design and implementation. *J Chronic Dis.* 1979;32(9-10):609-31. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease. *JAMA.* 1984;251(3):351-64.	Lipid Research Clinics Program Coronary Primary Prevention Trial

Appendix B4. Included Studies and Companion Papers

Primary publication	Other publications	Name of study/data source
Special populations – diabetes		
Lyerly et al, 2008[114]	None	Aerobic Center Longitudinal Study
Rutter et al, 2002[123]	Rutter MK, McComb JM, Brady S, Marshall SM. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *Am J Cardiol.* 1999;83(1):27-31.	Clinic patients in England

Appendix B5. Excluded Studies From Prior USPSTF Evidence Reviews

Author, year	Source	Reason for exclusion
Allen et al, 1980[1]	2004 report	Did not adjust for ≥5 Framingham risk factors
Blumenthal et al, 1996[2]	Annals	Did not adjust for ≥5 Framingham risk factors
Cullen et al, 1982[3]	2004 report	Did not adjust for ≥5 Framingham risk factors
Cumming et al, 1975[4]	2004 report	Did not adjust for ≥5 Framingham risk factors
Dunn et al, 1990[5]	2004 report	Did not adjust for ≥5 Framingham risk factors
Froelicher et al, 1974[6]	2004 report	Did not adjust for ≥5 Framingham risk factors
Frolkis et al, 2003[7]	*Annals*	>15% of patients with history of CHD at baseline
Gibbons et al, 2000[8]	*Annals*	Did not adjust for ≥5 Framingham risk factors
Hames et al, 1993[9]	2004 report	Adjusted hazard ratios not reported
Jones et al, 2002[10]	2004 report	Did not adjust for ≥5 Framingham risk factors
Kannel and Abbott, 1986[11]	2004 report	Did not adjust for ≥5 Framingham risk factors
Kannel et al, 1987[12]	2004 report	Did not adjust for ≥5 Framingham risk factors
Kannel and Cobb, 1992[11]	2004 report	Did not adjust for ≥5 Framingham risk factors
Katzel et al, 1999[13]	*Annals*	Did not adjust for ≥5 Framingham risk factors
Knutsen et al, 1988[14]	2004 report	Did not adjust for ≥5 Framingham risk factors
McHenry et al, 1984[15]	2004 report	Did not adjust for ≥5 Framingham risk factors
Pedoe, 1978[16]	2004 report	Did not adjust for ≥5 Framingham risk factors
Rabkin et al, 1982[17]	2004 report	Did not adjust for ≥5 Framingham risk factors
Reunanen et al, 1978[18]	2004 report	Did not adjust for ≥5 Framingham risk factors
Rose et al, 1978[19]	2004 report	Did not adjust for ≥5 Framingham risk factors
Sullivan et al, 1993[20]	2004 report	Did not adjust for ≥5 Framingham risk factors
Verdecchia et al, 2000[21]	2004 report	Did not adjust for ≥5 Framingham risk factors

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Appendix B7. Quality Rating Criteria for Studies Assessing ECG Abnormalities and Risk of Subsequent Cardiovascular Events*

Criteria:

- Was the cohort assembled at a uniform point (inception)?
- Did the study attempt to enroll consecutive patients or a random sample?
- Did the study adequately describe baseline demographic characteristics (at least age, sex, and race)?
- Was loss to followup low (<20%) and similar?
- Were outcomes measured using equal, reliable, and valid methods?
- Did the study clearly describe the screening test and methods for classifying results?
- Did the study analyze outcomes in patients with uninterruptable screening test results?
- Was the analysis adjusted for potential confounders?

*Adapted from Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20(3 Suppl):21-35.

Appendix C1. Quality Ratings: Cohort Studies of Resting ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Bodegard et al, 2004[66]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	No (22/2014 excluded)	Yes	5	Good
Brown, et al, 2000[67]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Fair
Crow, et al, 2003[68]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair
Cuddy et al, 2006[69] Other sources: www.mfus.ca	Unclear	Unclear	Yes	Low overall: Unclear Differential: Unclear	Unclear	Yes	Unclear	Yes	5	Fair
Daviglus et al, 1999[70] Other publications: Oglesby, 1963[146]	Yes	Unclear	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	5	Fair
De Bacquer et al, 1998[71]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	7	Good
Denes et al, 2007[72]	Yes	Yes	Yes	Low overall: Yes Differential: Unclear	Yes	Yes	No	Yes	6	Good
Dhingra et al, 2006[73]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Yes	Yes	7	Good
Diercks et al, 2002[74]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Fair
Gottdiener et al, 2000[75] Other publications: Furberg et al, 1992[147]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Good

Appendix C1. Quality Ratings: Cohort Studies of Resting ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Greenland et al, 2003[76]	Yes	Unclear	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Fair
Jouven et al, 2005[78]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Kahn et al, 1996[79]	Yes	Unclear (recruited volunteers)	Yes	Low overall: Yes Differential: Unclear	Unclear	Yes	Unclear	Yes	5	Fair
Larsen et al, 2002[80]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Liao et al, 1988[81]	Yes	Yes	Yes (blacks excluded from analysis)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	5	Fair
Macfarlane et al, 2007[77]	Yes	Yes	No (race not reported)	Low overall: Yes (12%) Differential: Yes	Yes	Yes	Unclear	Yes	4	Fair
Machado et al, 2006[82] Other publications: ARIC Investigators, 1989[148]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	No	Yes	7	Fair
Massing et al, 2006[83]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	No	Yes	7	Fair
Menotti et al, 1997[84] Other publications: RIFLE Research Group, 1993[149]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair
Menotti et al, 2001[85] Other publications: Menotti et al, 1996[156]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair

Appendix C1. Quality Ratings: Cohort Studies of Resting ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Moller et al, 2007[86]	Yes	Yes	No (race not reported)	Low overall: No (27%) Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair
Prineas et al, 2001[87]	Yes	Yes	Yes	Low overall: Yes Differential: Unclear	Yes	Yes	Unclear	Yes	5	Good
Prineas et al, 2002[88]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	7	Good
Rautaharju et al, 2006a and 2006b[89,90]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Unclear	Yes	No (excluded at baseline)	Yes	5	Fair
Rautaharju et al, 2006c[91]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	No (excluded at baseline)	Yes	5	Fair
Sigurdsson et al, 1996[92]	Yes	Yes	No (race not reported)	Low overall: No Differential: Unclear	Unclear	Yes	Unclear	Yes	6	Fair
Sutherland et al, 1993[93]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good

Appendix C2. Quality Ratings: Cohort Studies of Exercise ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Aktas et al, 2004[95]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	No	Yes	7	Fair
Adabag et al, 2008[94]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	7	Good
Balady et al, 2004[96] Other publications: Framingham Study[150]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	7	Good
Blair et al, 1996[97] Other publications: Wei et al, 1999[151]	Unclear	Unclear	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair
Bodegard et al, 2004[66]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	No (22/2014 excluded)	Yes	5	Good
Cole et al, 2000[98]	Yes	No	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Cournot et al, 2006[99]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Good
Ekelund et al, 1989[100]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Yes	Yes	6	Good
Fleg et al, 1990[101]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	No	Yes	6	Good
Giagnoni et al, 1983[102]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	5	Good
Gordon et al, 1986[103]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Unclear	Yes	No	Yes	7	Fair
Gulati et al, 2003[105]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair

Appendix C2. Quality Ratings: Cohort Studies of Exercise ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Gulati et al, 2005[104] Same population as Gulati et al, 2003[105]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	No (excluded)	Yes	7	Good
Josephson et al, 1990[106]	No	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair
Jouven et al, 2000[107] Other publications: Filipovsky et al 1992[152]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Jouven et al, 2005[78]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Kurl et al, 2003[108]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Fair
Kurl et al, 2009[109]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair
Lauer et al, 1996[110]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair
Laukkanen et al, 2001[111]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Laukkanen et al, 2006[112]	Yes	Yes	No (race not reported)	Low overall: Yes Differential: Yes	Yes	Yes	No	Yes	7	Good
Lyerly et al, 2008[114]	Yes	Unclear	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Fair

Appendix C2. Quality Ratings: Cohort Studies of Exercise ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Lyerly et al, 2009[115]	Yes	Unclear	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Fair
Mora et al, 2003[116]	Yes	No (mixed population; 15% random selection)	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	6	Good
Mora et al, 2005[117]	Yes	Yes	Yes	Low overall: Unclear Differential: Unclear	Yes	Yes	No	Yes	6	Fair
Morshedi-Meibodi et al, 2002[118]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Unclear	Yes	Unclear	Yes	7	Fair
Okin et al, 1991[119]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	No	Yes	6	Good
Okin et al, 1996[120]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	No	Yes	5	Fair
Rautaharju et al, 1986[122]	Yes	Yes	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Unclear	Yes	5	Good
Rutter et al, 2002[123] Other publications: Rutter et al, 1999[153]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair
Rywik et al, 1998[124]	No	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	6	Good
Rywik et al, 2002[125]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	No (those unable to achieve ≥85% of max predicted HR on exercise and MN code 11.3 excluded)	Yes	5	Fair

Appendix C2. Quality Ratings: Cohort Studies of Exercise ECG

Author, year	Cohort assembled at a uniform point	Enrolled consecutive patients or a random sample	Described baseline demographic characteristics	Loss to followup was low (<20%) and similar	Outcomes measured using equal, reliable, and valid methods	Described screening test and methods for classifying results	Analyzed outcomes in patients with uninterpretable screening test results	Adjusted analysis	Number of Framingham risk score variables adjusted	Quality rating
Savonen et al, 2007[126]	Yes	Yes	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	7	Fair
Siscovick et al, 1991[127] Other publications: Lipid Research Clinics Program 1984[154]	Yes	Unclear (all patients had high cholesterol	Yes	Low overall: Yes Differential: Yes	Yes	Yes	Yes (included with negative test results)	Yes	5	Good
Sui et al, 2007[129]	Yes	Unclear	No (race not reported)	Low overall: Unclear Differential: Unclear	Yes	Yes	Unclear	Yes	5	Fair